



pituitary  
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# **ACROMEGALY UPDATE**

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Cedars-Sinai Medical Center, Los Angeles, CA, USA

**OCTOBER 2021**

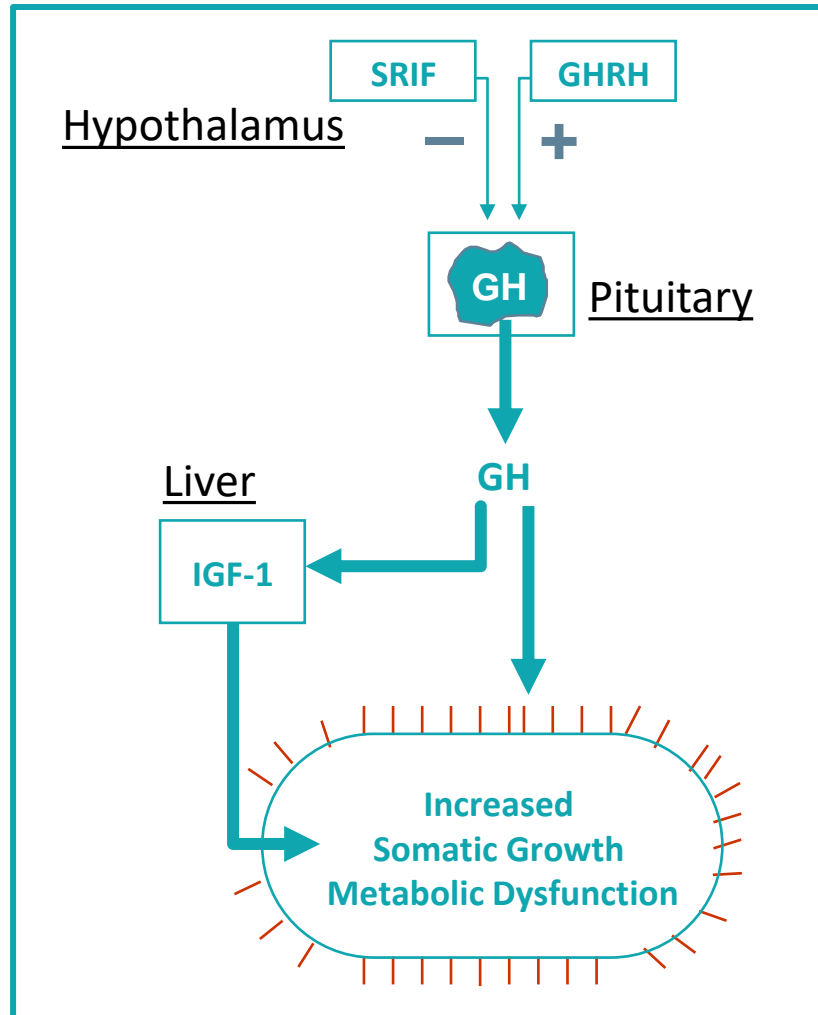
# ACROMEGALY UPDATE



# DISCLOSURES

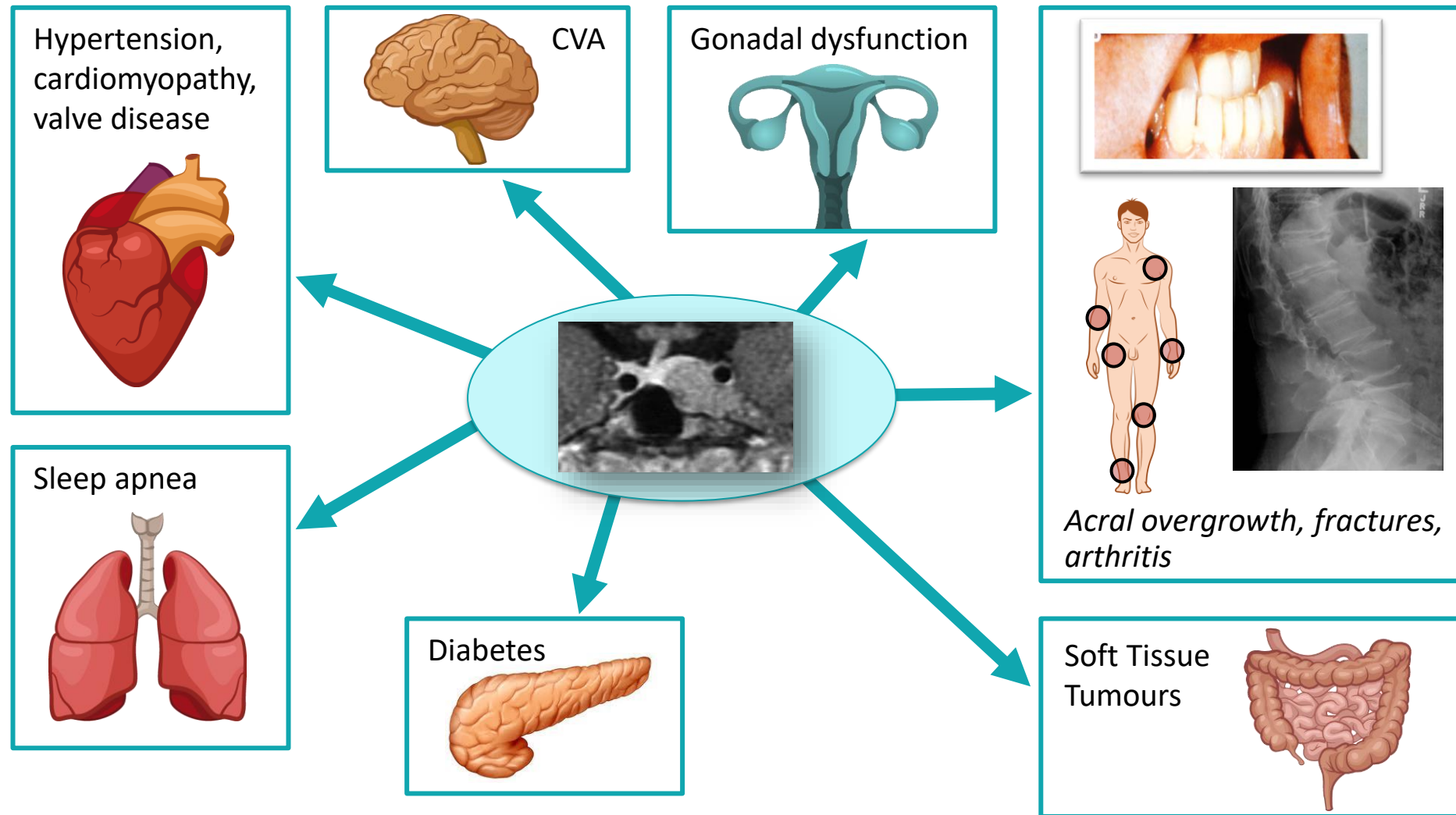
- Investigator-initiated clinical trial support from Pfizer
- Consultant to Chiasma, Crinetics, Ionis, Ipsen, Novo Nordisk

# GH-SECRETING ADENOMA: PERSISTENT GH AND IGF-1 EXCESS

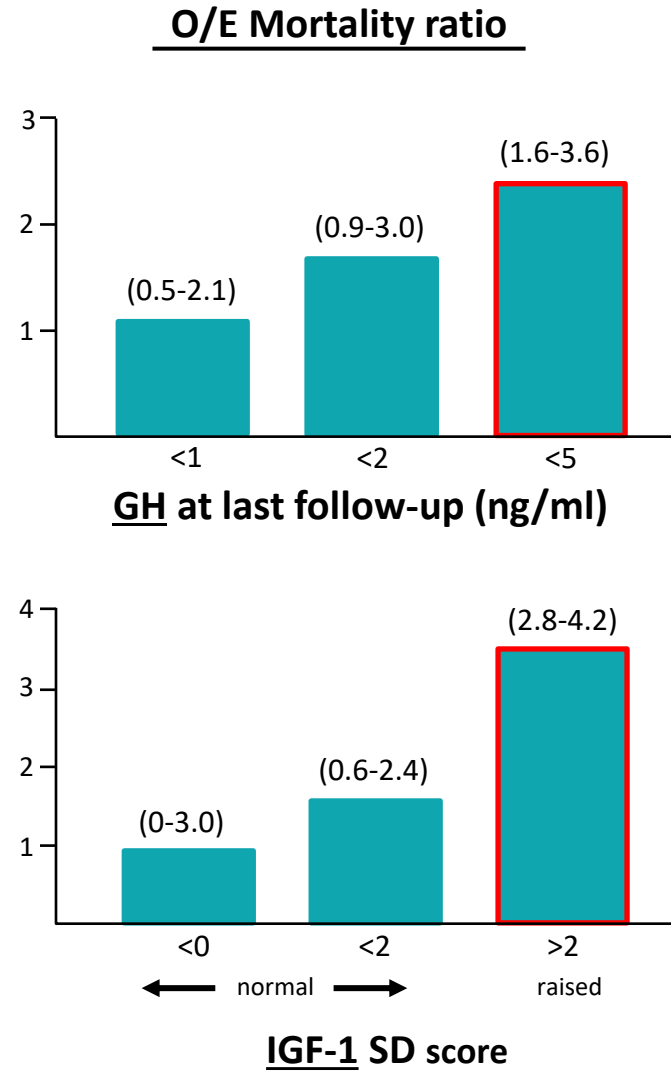


- Chronic GH excess, from **pituitary adenoma**
- **Advanced disease at diagnosis due to impact of chronic GH/IGF-1 exposure**
- **Co-morbidities** if chronically uncontrolled
- Integrated management

# IMPACT OF GH AND IGF-1 EXCESS

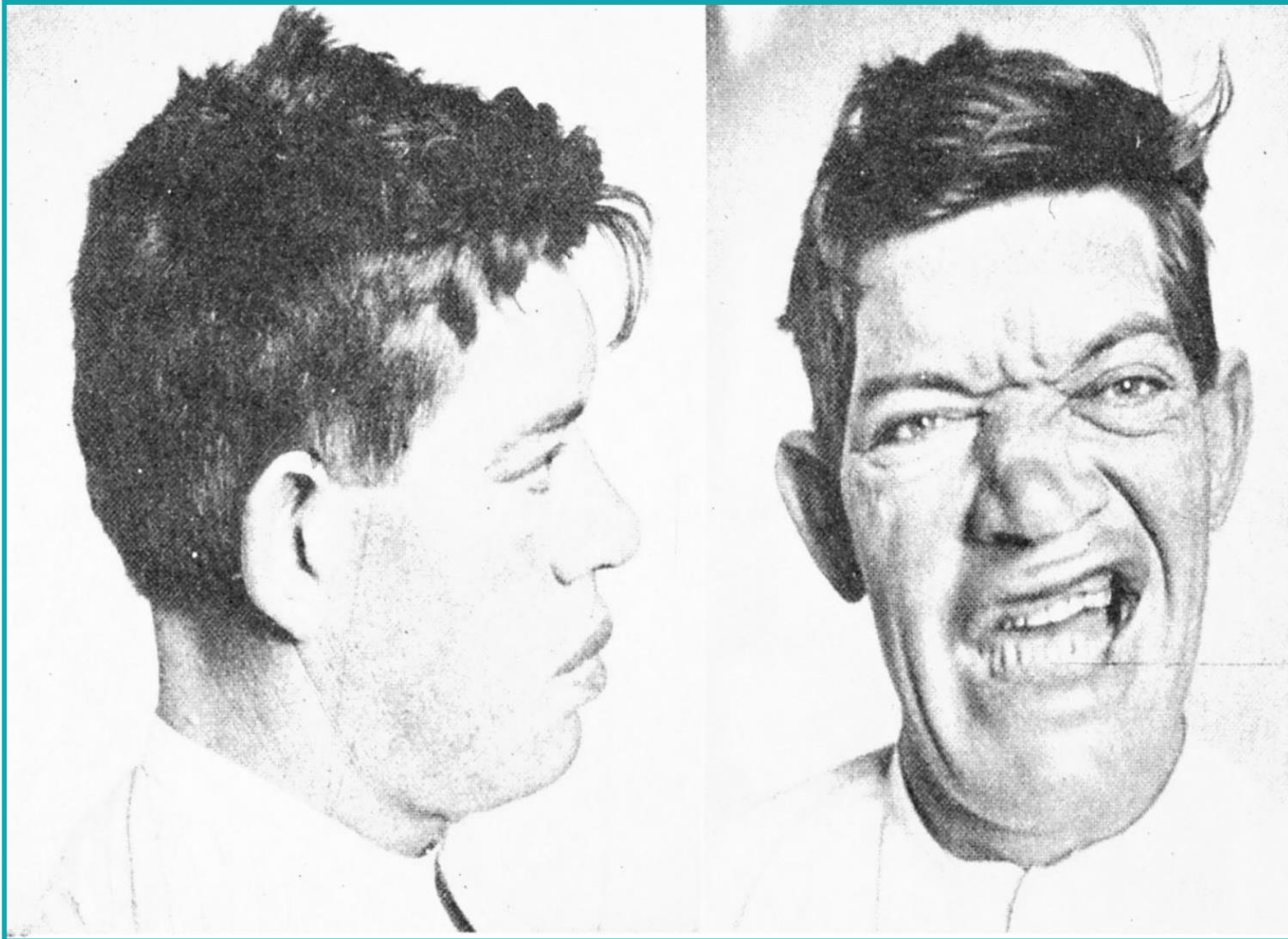


# GH AND IGF-1 ASSOCIATE WITH MORTALITY



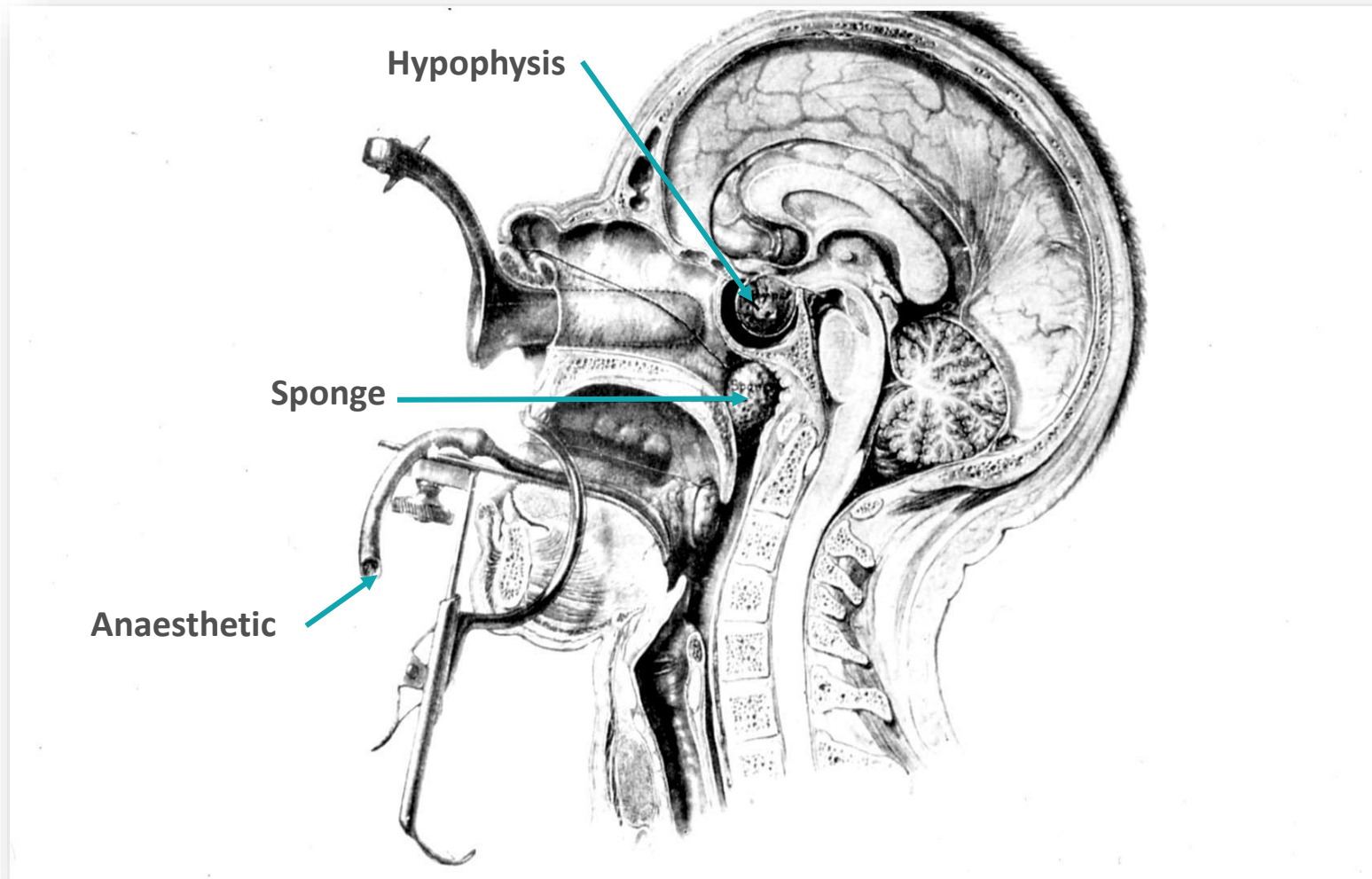


**Left**, showing marked frontal protrusion, thick lips, etc., in profile

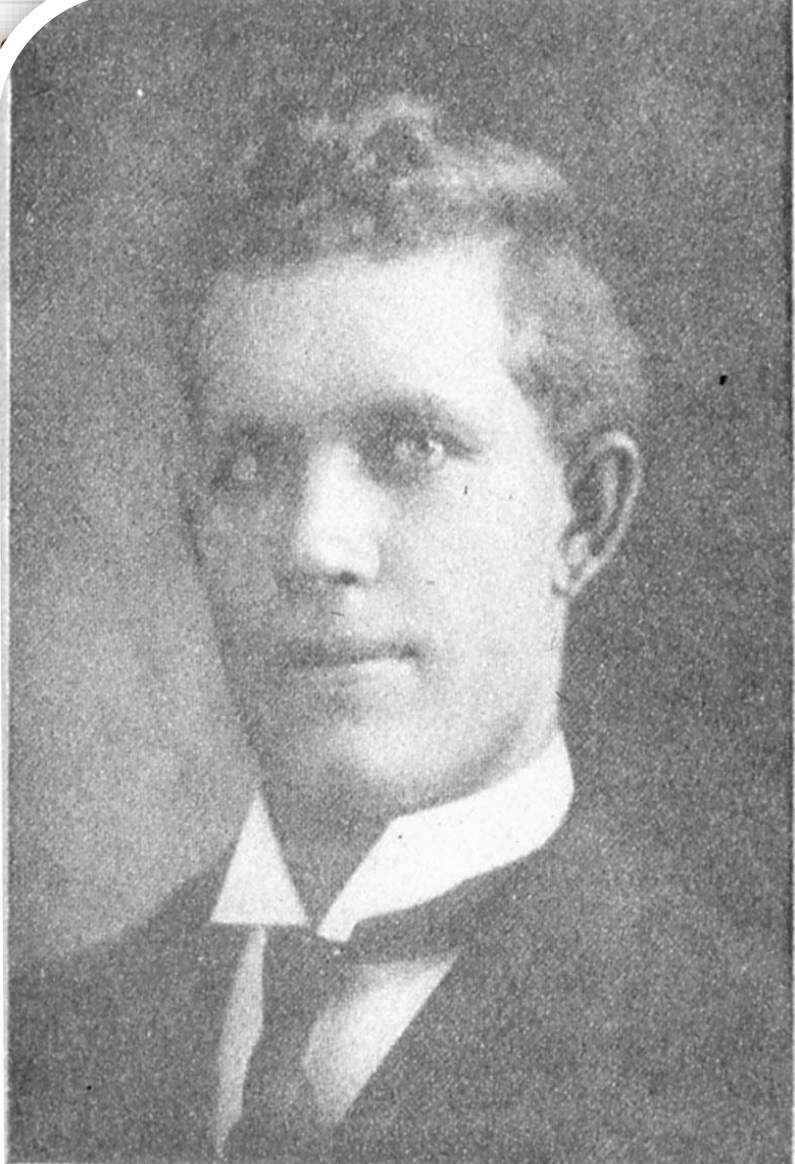


**Right**, patient in the act of showing teeth while jaws which meet only on the right are held closed. Note the deep furrows of the thickened cutaneous tissues





- Cushing's sublabial, transseptal pituitary operation. Self-retaining bivalved speculum is in place beneath nasal mucosa

8. Case XXXVIII.....	May 1		h day. ry com-	Early acromegaly. Cerebellar cyst: internal hydrocephalus
9. Case II.....	June		nd day edullary ms	Chromophobe struma with intracranial extension. Acromegaly
10. Case XXIX.....	June		nprove-	Stationary advanced acromegaly with polyglandular signs
11. Case XXX.....	July		ered	Advanced acromegaly with hypopituitarism
12. Case XIX.....	(1) July		ered	Chromophobe struma with dyspituitarism
	(2) Aug.		nprove- restora- vision	
13. Case XX.....	Oct.		: resto- f vision	Interpeduncular cyst or tumor (uncertified)
14. Case XXXVII.....	Oct.		: resto- f vision	Interpeduncular cyst or tumor (uncertified): adiposis dolorosa
15. Case IV.....	Nov.		ved	Interpeduncular tumor. Infantilism
16. Case I.....	Dec.		ved	Chromophobe struma with dyspituitarism. Acromegalic gigantism
Case V.....	Dec.		th	Chromophobe struma with intracranial extension. Adiposo-genital dystrophy
Case VII.....	(1) Jan.		roved	Interpeduncular tumor (uncertified) with hypopituitarism
	(2) Mar.		pressure ms with of vision	

**Case 1.** Patient at 25, apparently free from acromegalic changes



# COMPREHENSIVE TREATMENT



## Goals:

- Eliminate morbidity
- Reduce mortality
- Enhance QOL

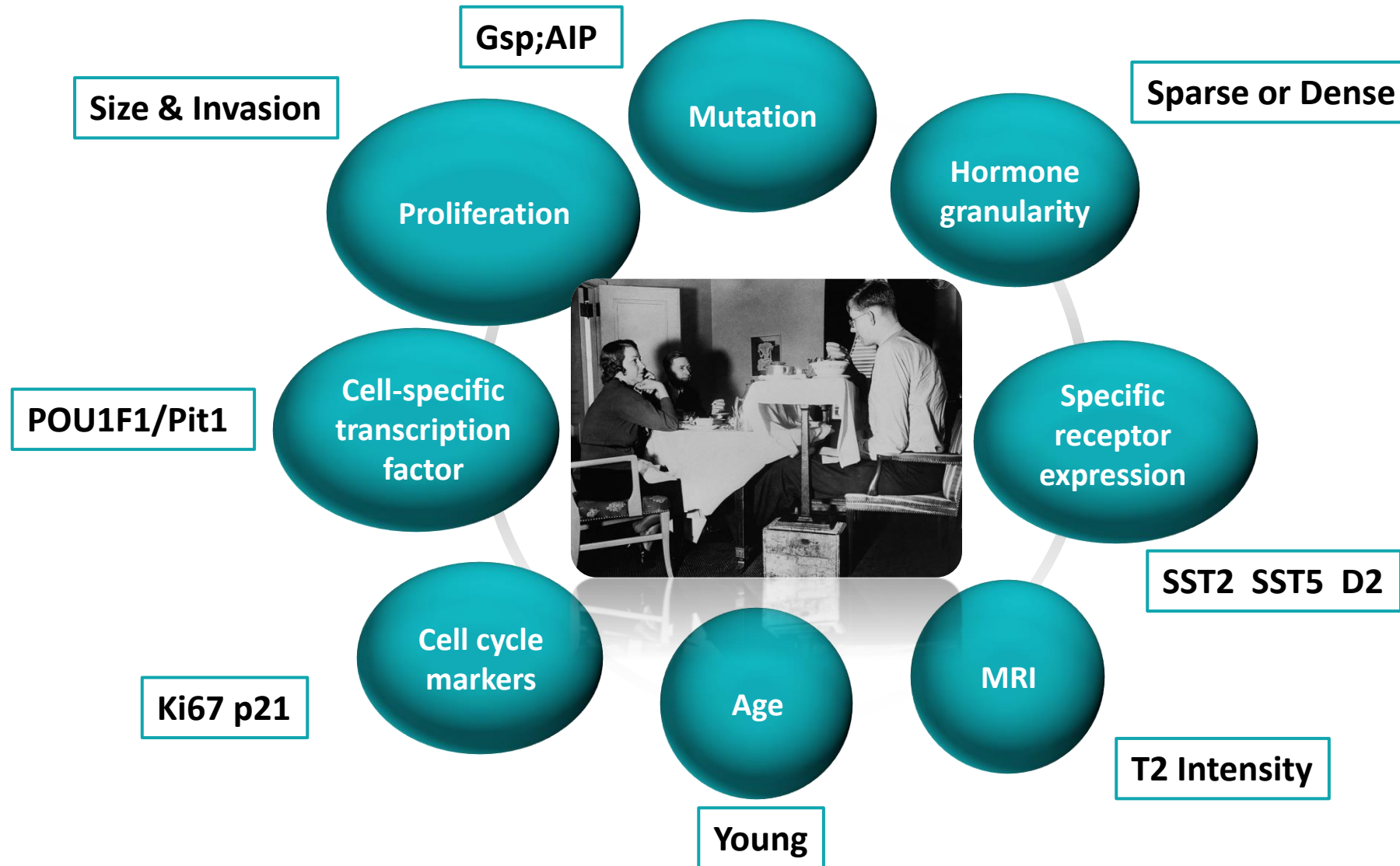
## Strategy:

- Safe
- Control mass effects
- Control GH secretion and action
- **Preserve** pituitary function

## Assessment:

- Age-adjusted IGF-1
- *Co-morbidity improvement*

# CAN WE PERSONALISE ACROMEGALY RX ?

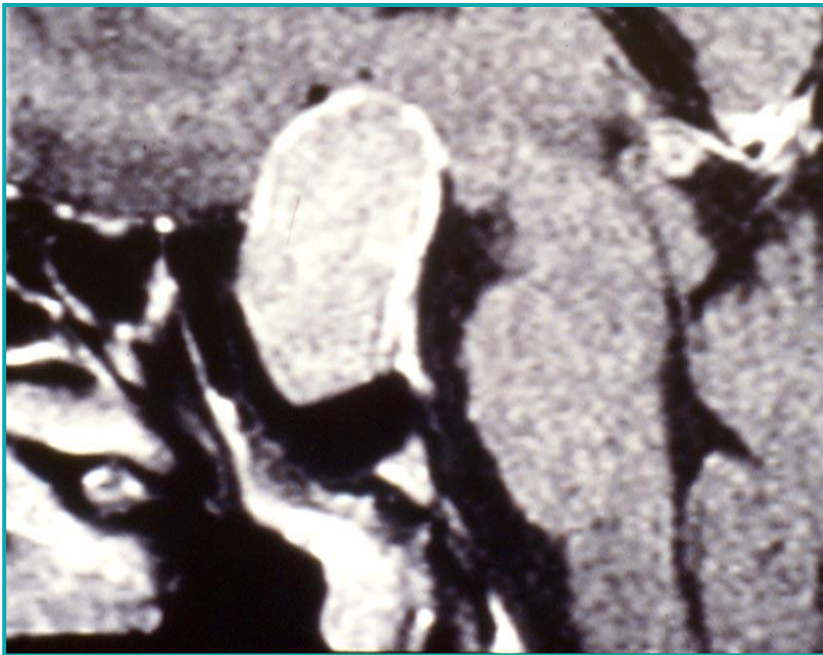


AIP, aryl hydrocarbon receptor-interacting protein; D2, dopamine D2 receptor; Gsp, G stimulatory proteins; MRI, magnetic resonance imaging; POU1F1/Pit1, POU domain class 1 transcription factor 1; Rx, therapy; SST2/5, somatostatin receptor type 2/5

Melmed S. J Clin Endocrinol Metab. 2016;101(3):769-77

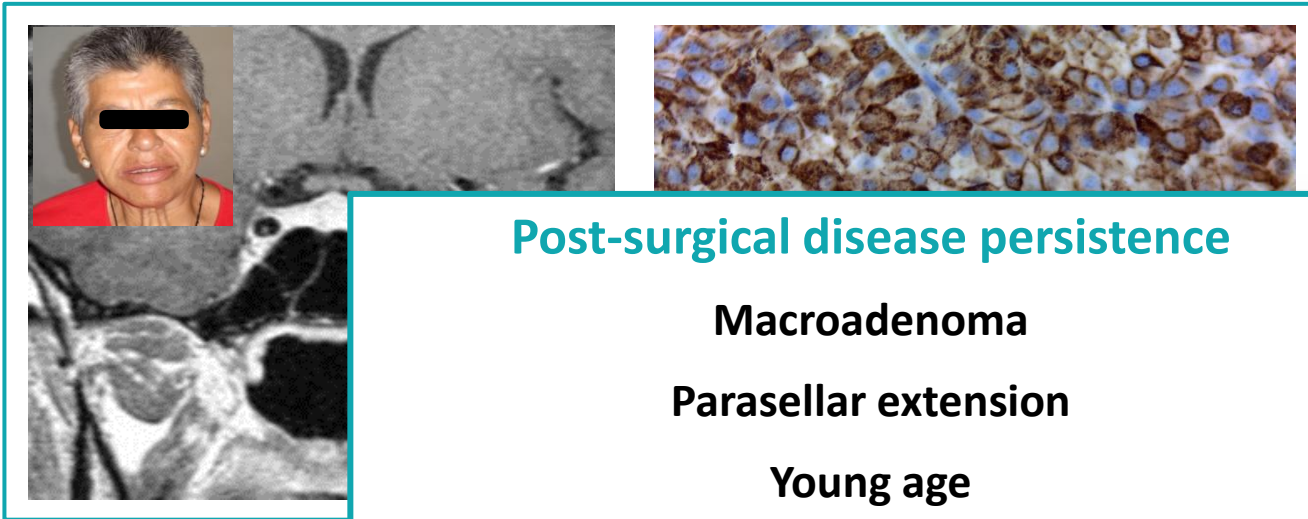
# 22-YEAR-OLD MALE: GH 42 NG/ML, IGF-1 900 NG/ML

- Is he a candidate for surgery?
- Does he exhibit tumour mass effects?
- Is the tumour resectable?

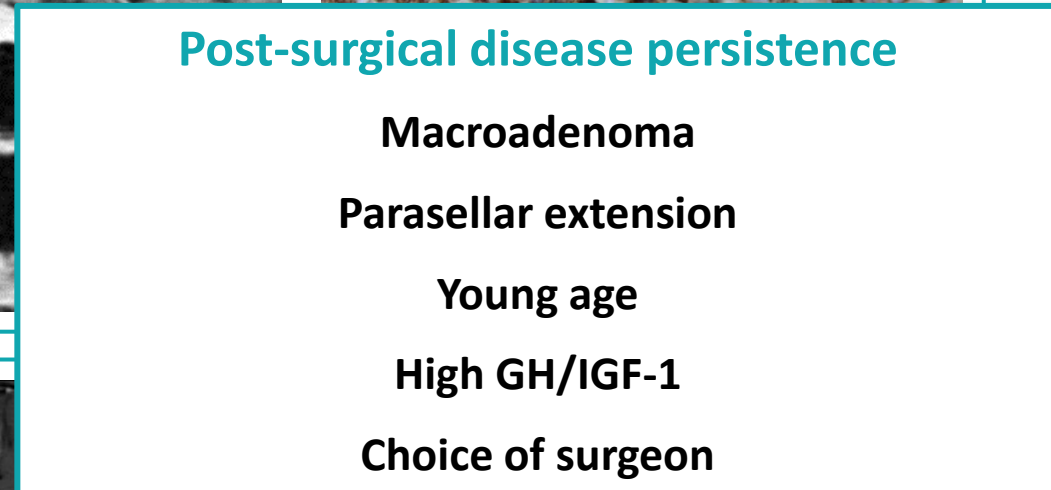
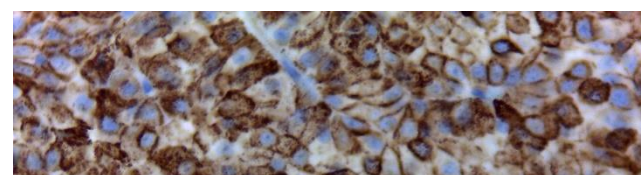




# ACROMEGALY SUBTYPES

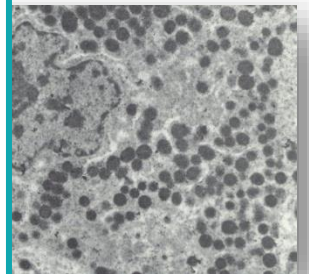


**Microadenoma**  
*Dense granulation*

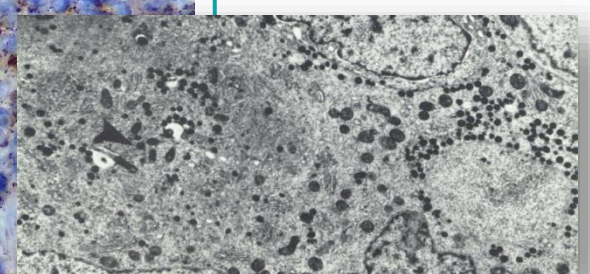
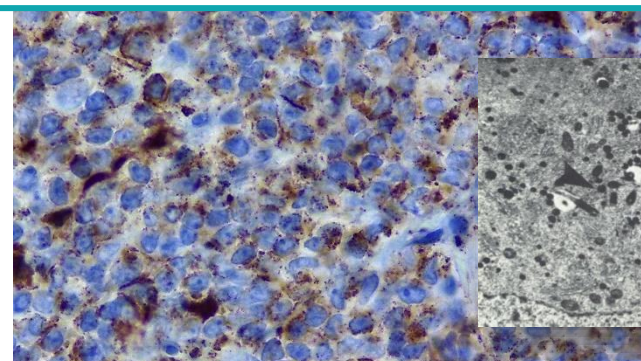
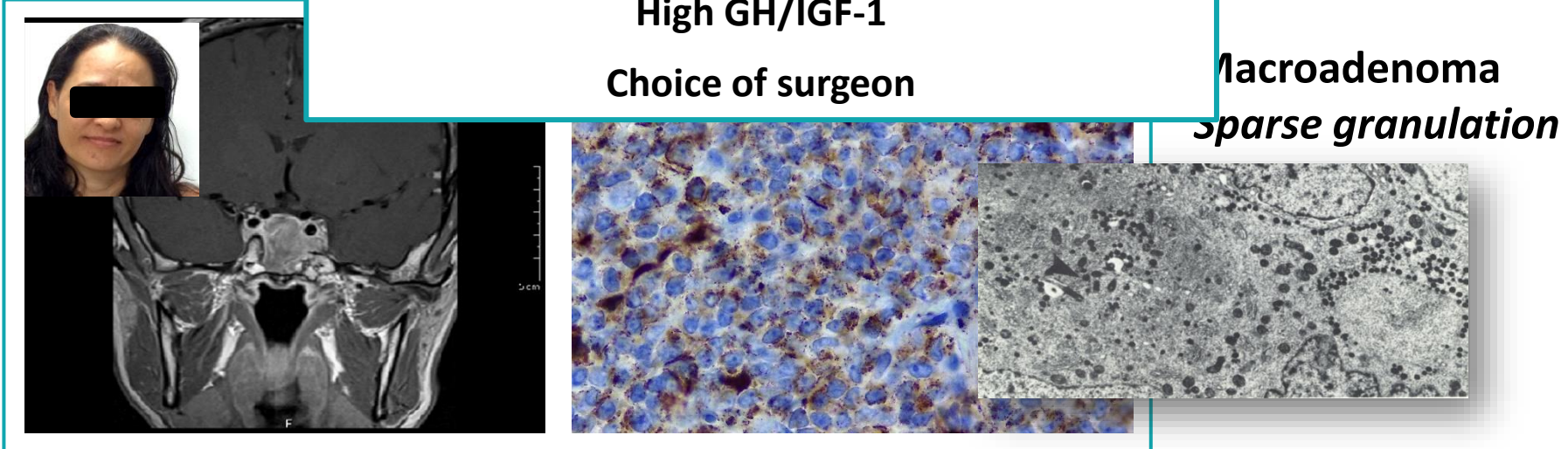


**Post-surgical disease persistence**

- Macroadenoma
- Parasellar extension
- Young age
- High GH/IGF-1
- Choice of surgeon



**Macroadenoma**  
*sparse granulation*

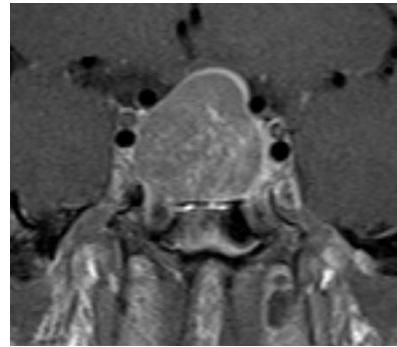


# 28-YEAR-OLD NEWLY DIAGNOSED ACROMEGALY



Excess sweating  
Jaw prognathism  
Headache  
Arthritis  
Hypertension

**IGF-1 950 ng/ml**



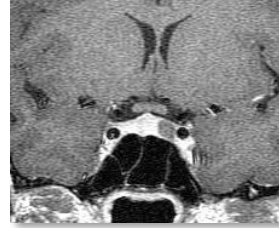
24 hrs after surgical resection of **sparsely granulated GH-secreting adenoma**, random **GH 2 ng/ml**

Six months later **IGF-1** levels 397 ng/ml (nl <275 ng/ml)

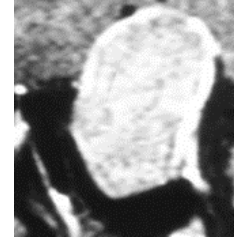


# ACROMEGALY CLASSIFICATION: PRECISE, PERSONALISED APPROACH TO THERAPY

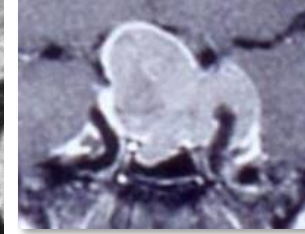
Type 1



Type 2



Type 3



		Type 1	Type 2	Type 3
<b>Frequency (%)</b>		50%	19%	31%
<b>Tumour</b>	<b>Size</b>	<i>Micro</i>	Macro	<i>Macro</i>
	<b>Invasiveness</b>	No	Intermediate	Yes
	<b>GH granulation</b>	<i>Dense</i>	Both	<i>Sparse</i>
<b>Immunoreactivity (%)</b>	Ki-67 <3%	90	33	42
	SST2	58	30	22
<b>Biochemistry</b>	IGF-1	<i>Lower</i>	<i>Intermediate</i>	<i>Higher</i>
<b>Outcomes</b>	No. of surgeries	1	1 or 2	≥2
	Control	Frequent	Intermediate	Rare

# CAN WE CLASSIFY A PRECISE, PERSONALISED APPROACH TO OPTIMAL OUTCOMES?

		Type 1	Type 2	Type 3
Frequency (%)		50%	19%	
Tumour	Size	<i>Micro</i>	Macro	 <ul style="list-style-type: none"> <li>• <b>Sparsely granulated aggressive macro</b></li> <li>• <b>Adverse outcomes, despite more treatments</b></li> <li>• <b>Young age</b></li> </ul>
	Invasiveness	No	Intermediate	
	<b>GH granulation</b>	<i>Dense</i>	Both	
Immunoreactivity (%)	Ki-67 <3%	90	33	
	SSTR2	58	30	
Biochemistry	IGF-1	<i>Lower</i>	<i>Intermediate</i>	<i>Higher</i>
Outcomes	No. of surgeries	1	1 or 2	≥2
	Disease control	Frequent	Intermediate	Rare

# ACROMEGALY MEDICAL RX

## SRL

Lanreotide autogel	60-120 mg SC q 4-8 wks
Pasireotide	40-60 mg IM q 4 wks
Octreotide LAR	10-40 mg IM q 4 wks
Oral octreotide	40-80 mg daily

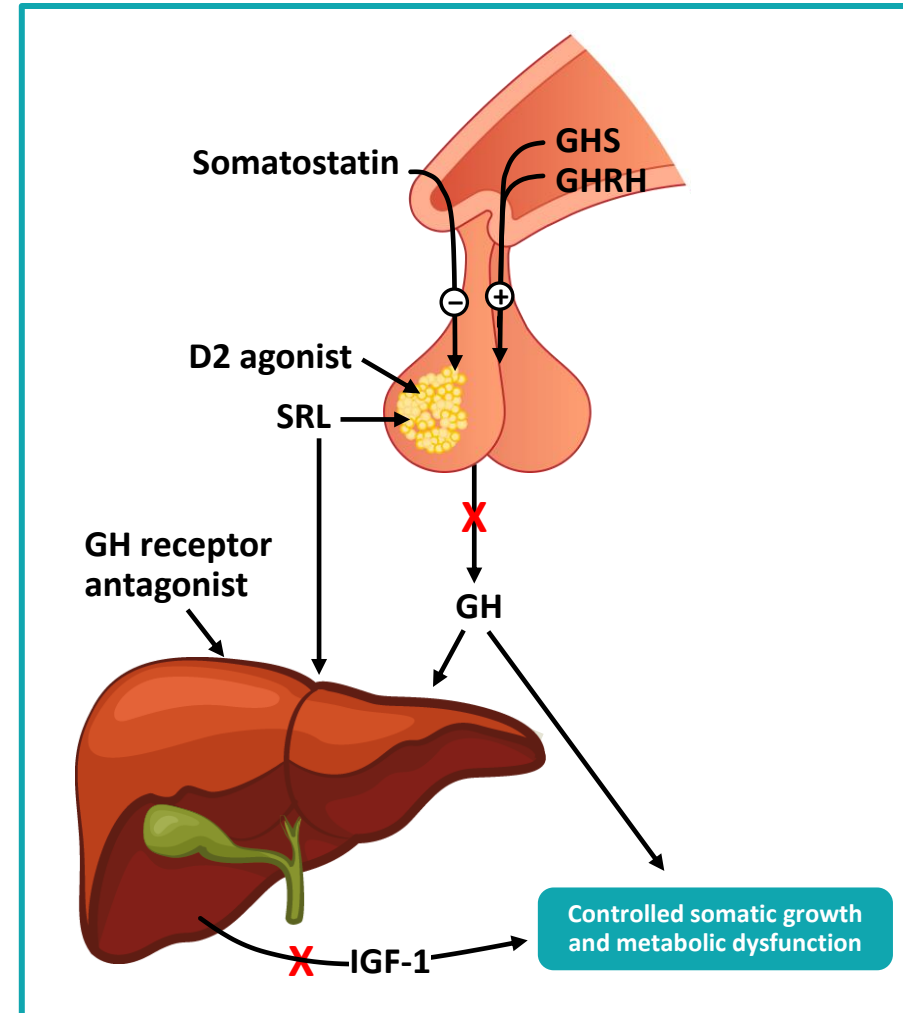
## D2 Agonist

Cabergoline	1-4 mg orally every wk
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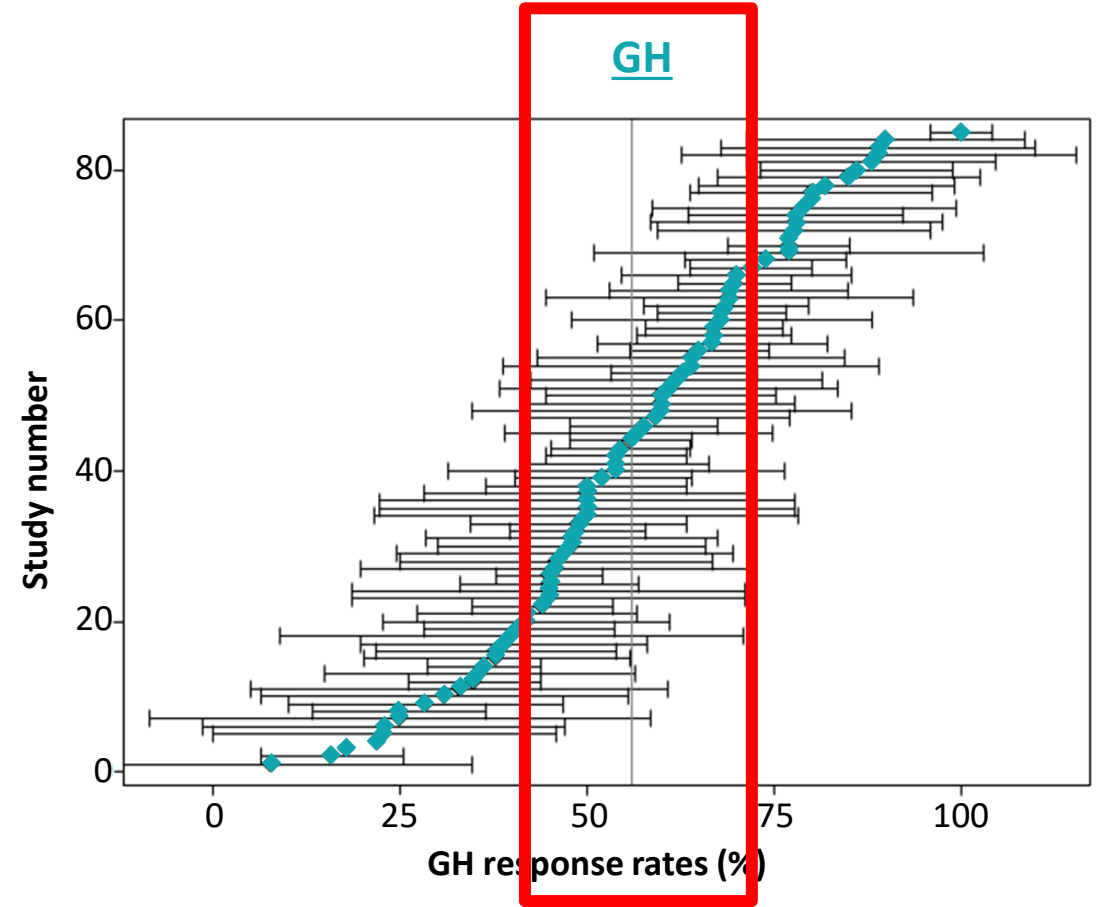
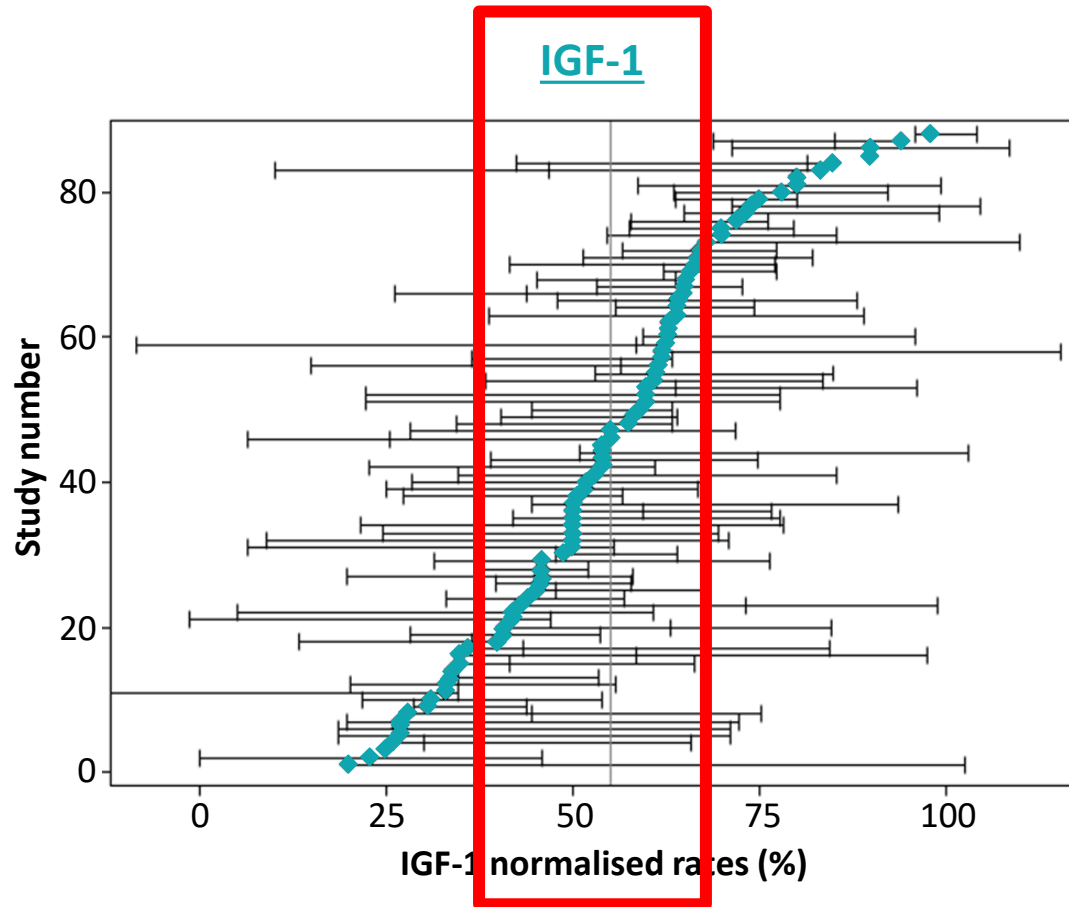
## GHR Antagonist

Pegvisomant	10-40 mg SC daily
-------------	-------------------

- Not disease modifying
- Individualised titrations or combinations
- Life-long

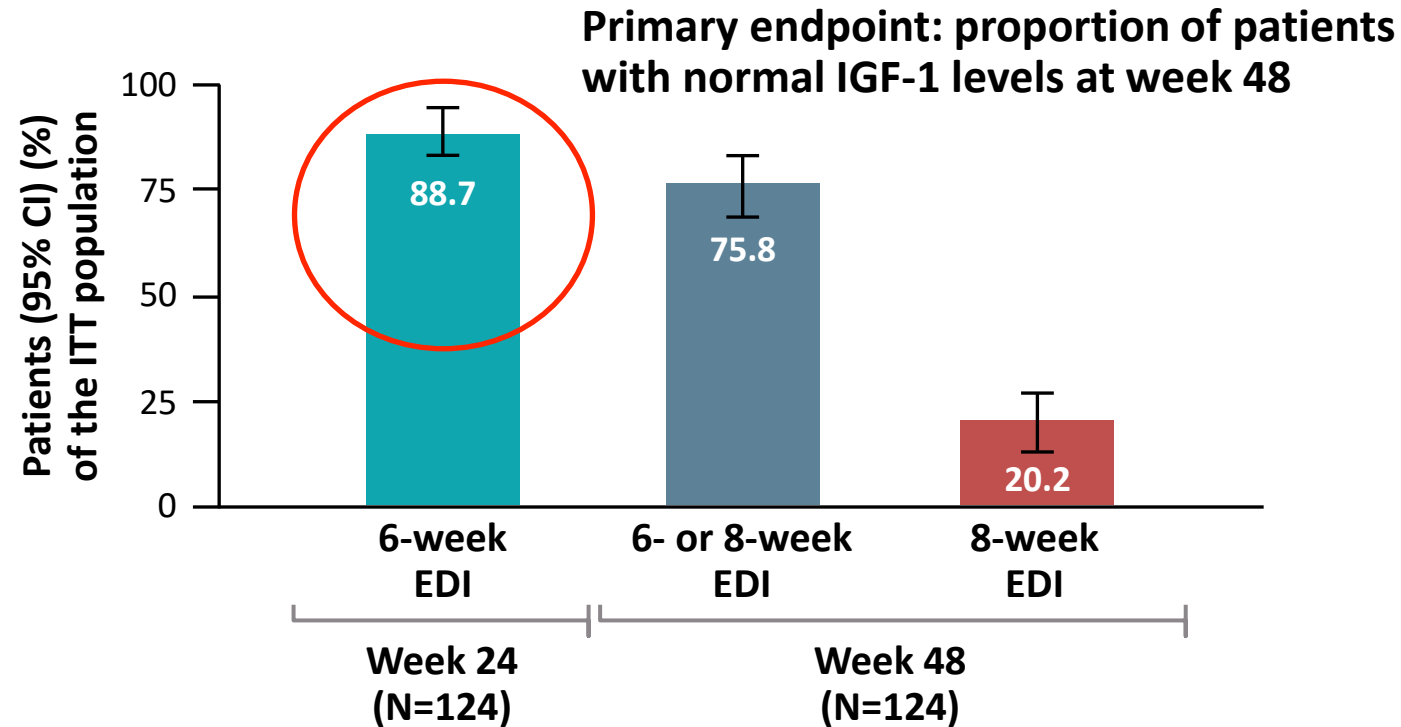


# META-ANALYSIS OF SRL RESPONSIVENESS



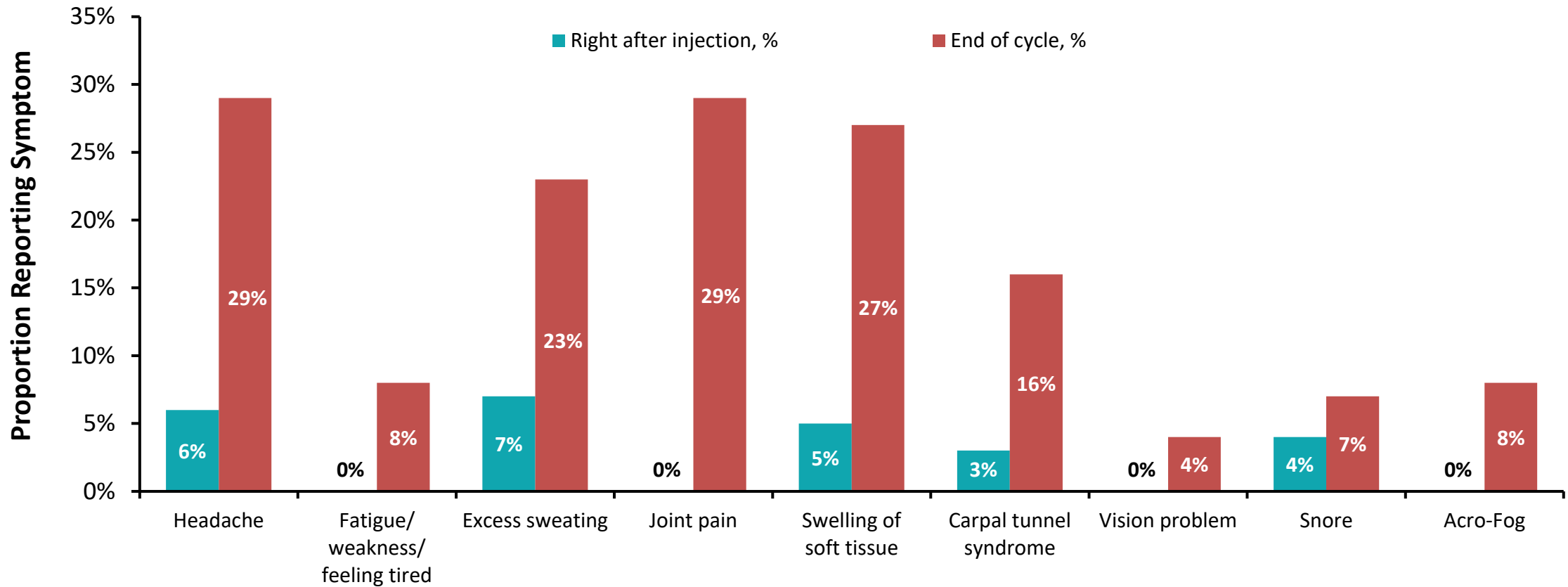
# NORMALISED IGF-1 ON EXTENDED DOSING INTERVALS

## EVALUATED EDIs WITH LANREOTIDE AUTOGEL 120 MG IN PATIENTS PREVIOUSLY CONTROLLED WITH OCTREOTIDE LAR 10 OR 20 MG



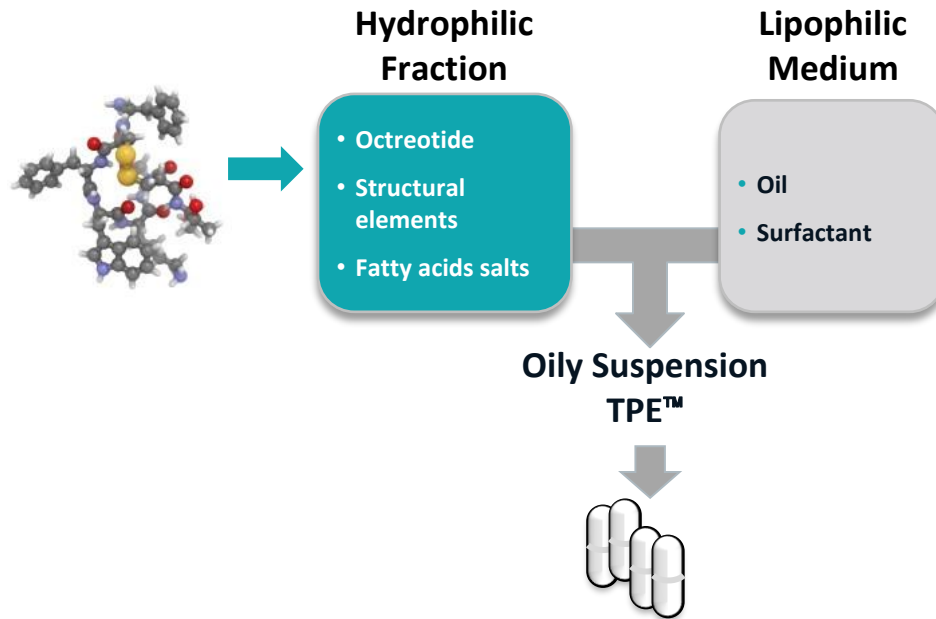
Lanreotide Autogel 120 mg at extended dosing intervals

# SYMPTOMS WORSEN AT END OF CYCLE

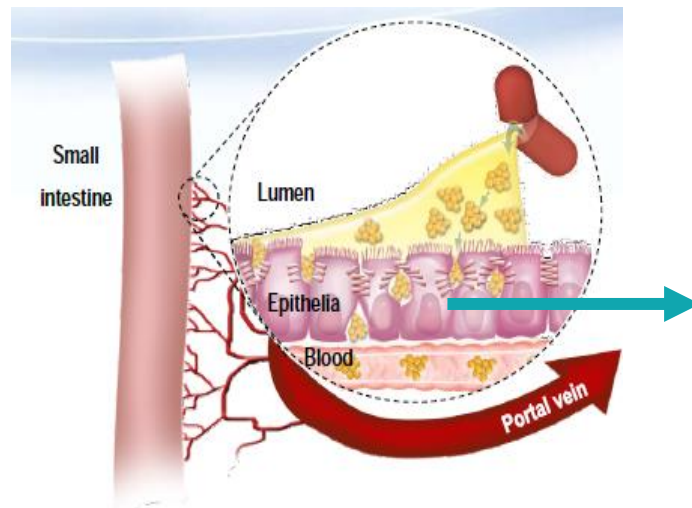


**52% of patients report worsening symptoms toward end of SRL dosing cycle**

# ORAL OCTREOTIDE



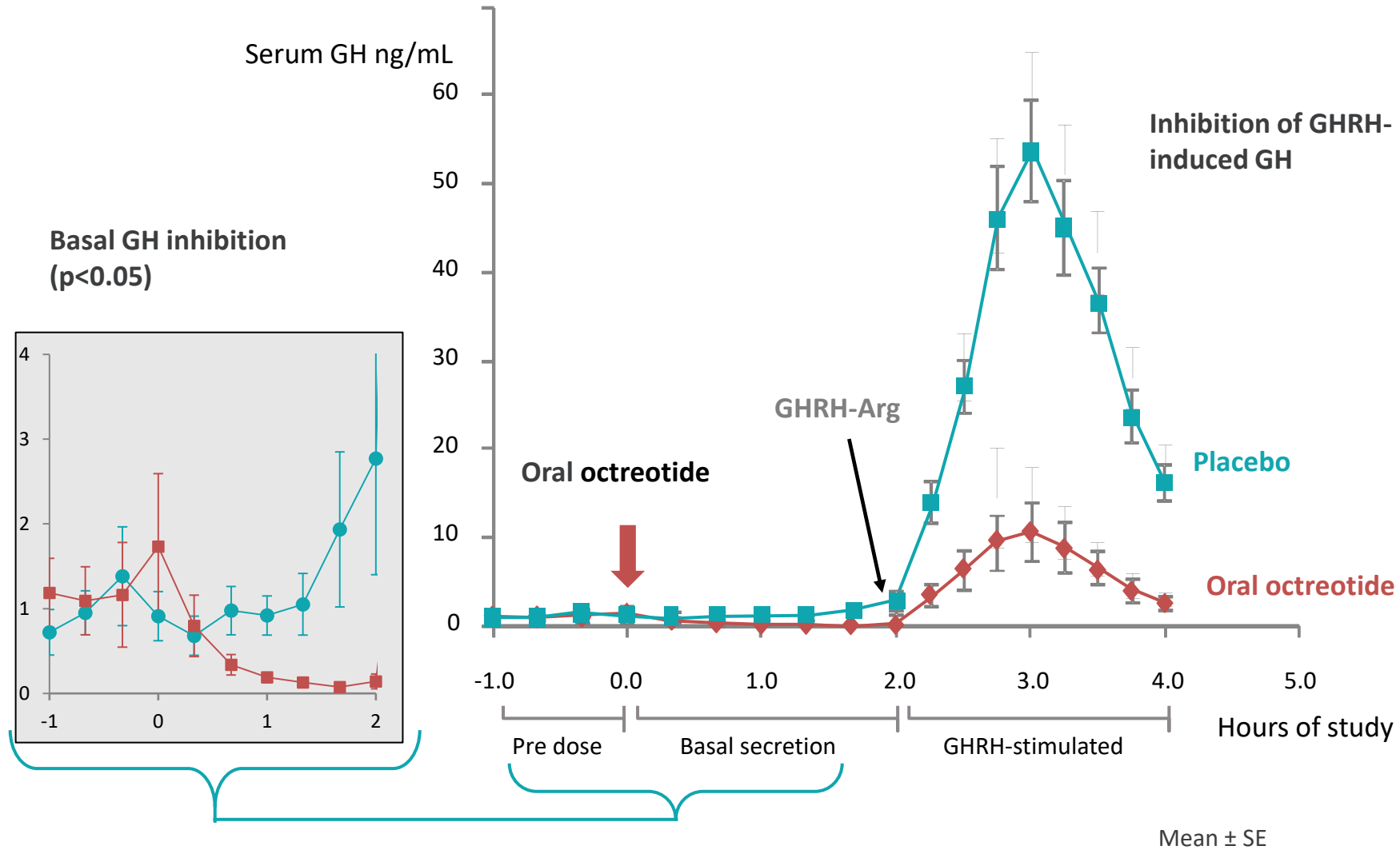
- TPE transiently opens tight junctions
- Excipients safe
- Octreotide not chemically modified



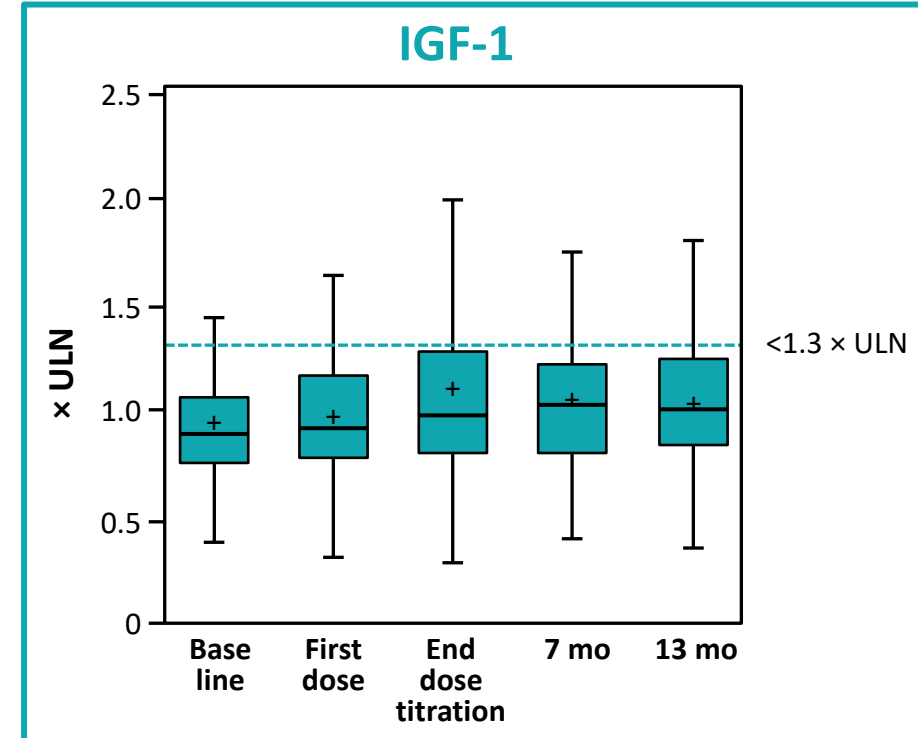
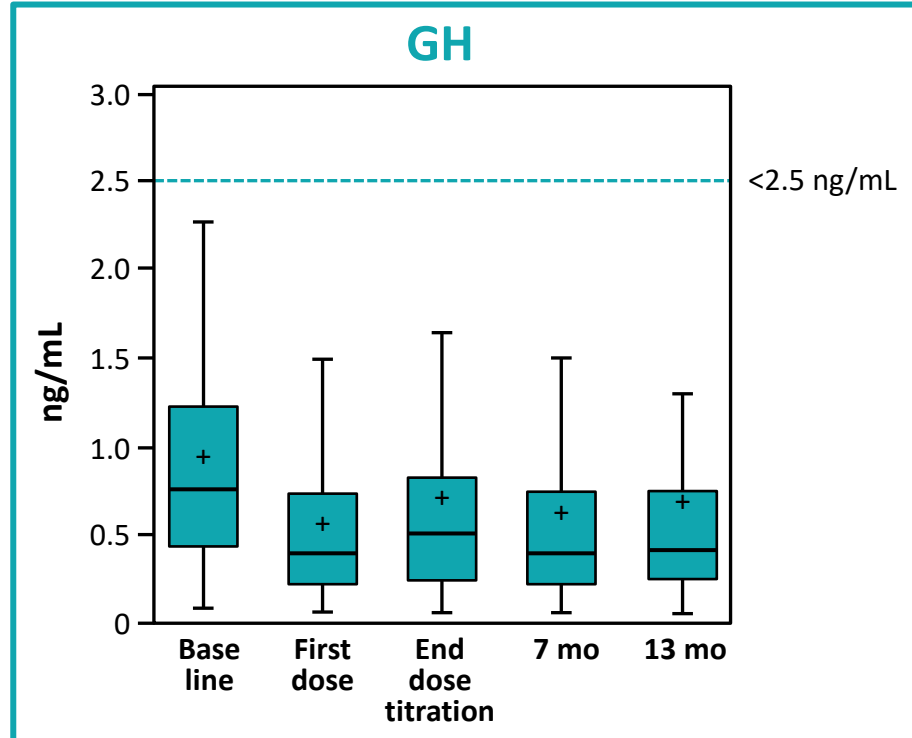
Tight junctions  
opened



# ORAL OCTREOTIDE IS BIOACTIVE IN 16 HEALTHY SUBJECTS

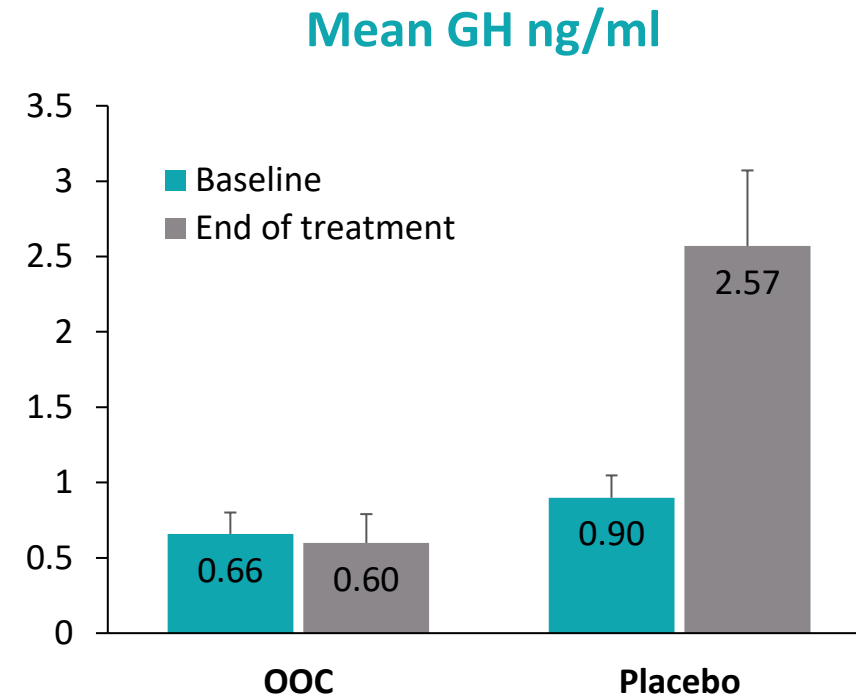
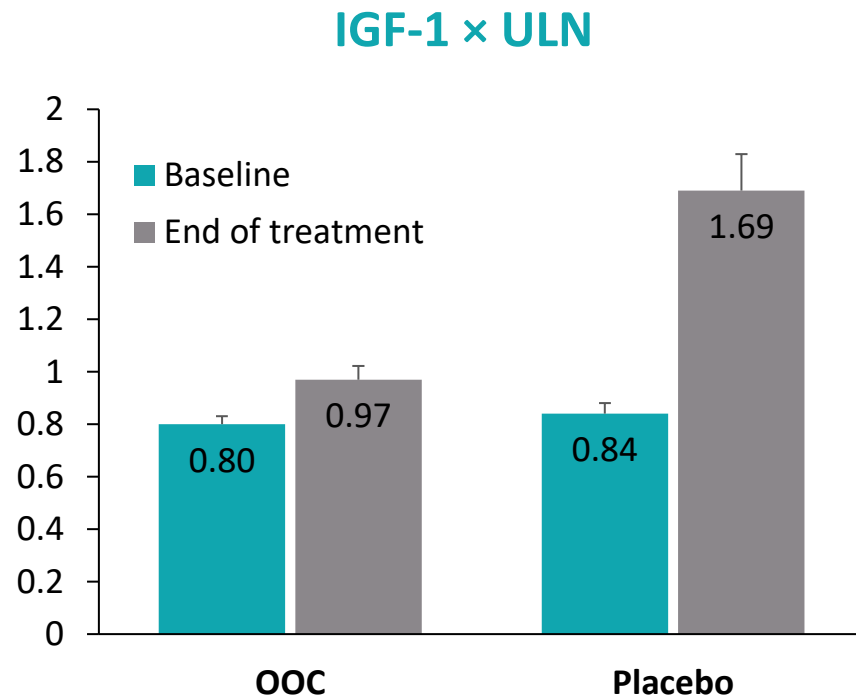


# OPEN-LABEL TRIAL: DESCRIPTIVE ENDPOINTS



**Sustained biochemical response in all dosed patients (n=151)**

# OPTIMAL DOUBLE-BLIND PLACEBO CONTROL: PHASE 3

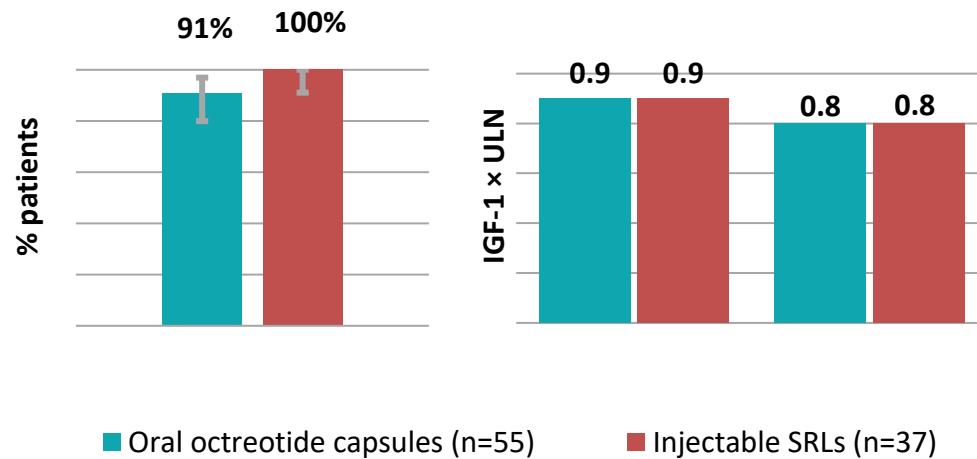


OOC efficacy and safety in 56 patients previously controlled on injectable SRLs

## Biochemical control at 36 weeks

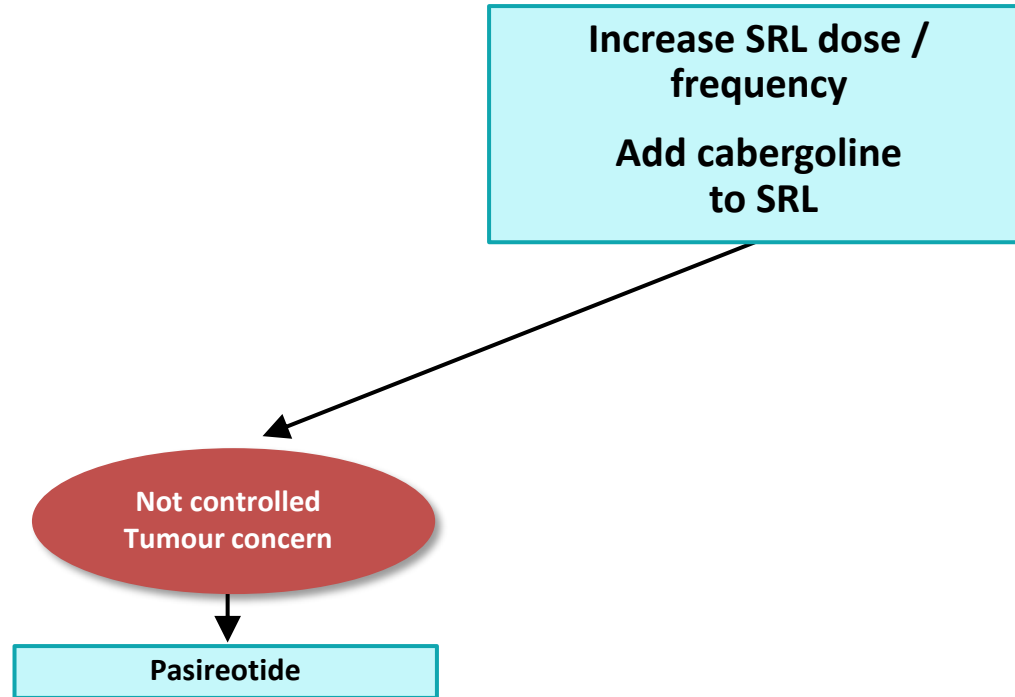
# MPOWERED STUDY: ORAL OCTREOTIDE VS INJECTABLE SRLS

## NON-INFERIORITY WITH STABLE IGF-1 DURING 36 WEEKS

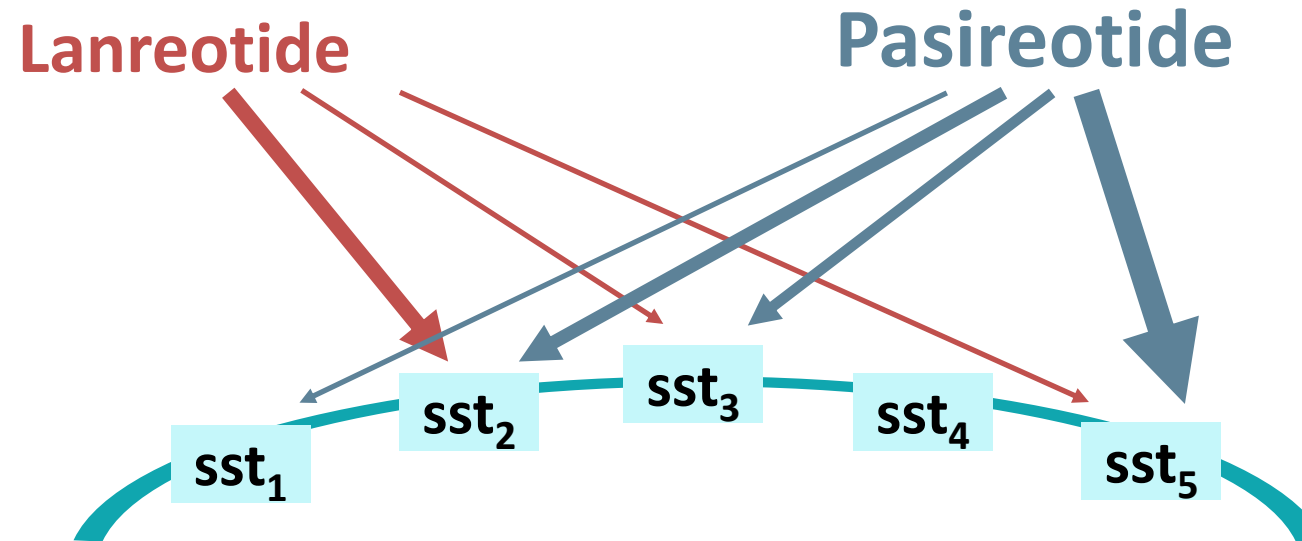


- Patient-reported improvements after switching from injectable to oral SRL
  - Fatigue
  - Swelling
  - Rx convenience
  - Rx satisfaction

# INADEQUATE CONTROL

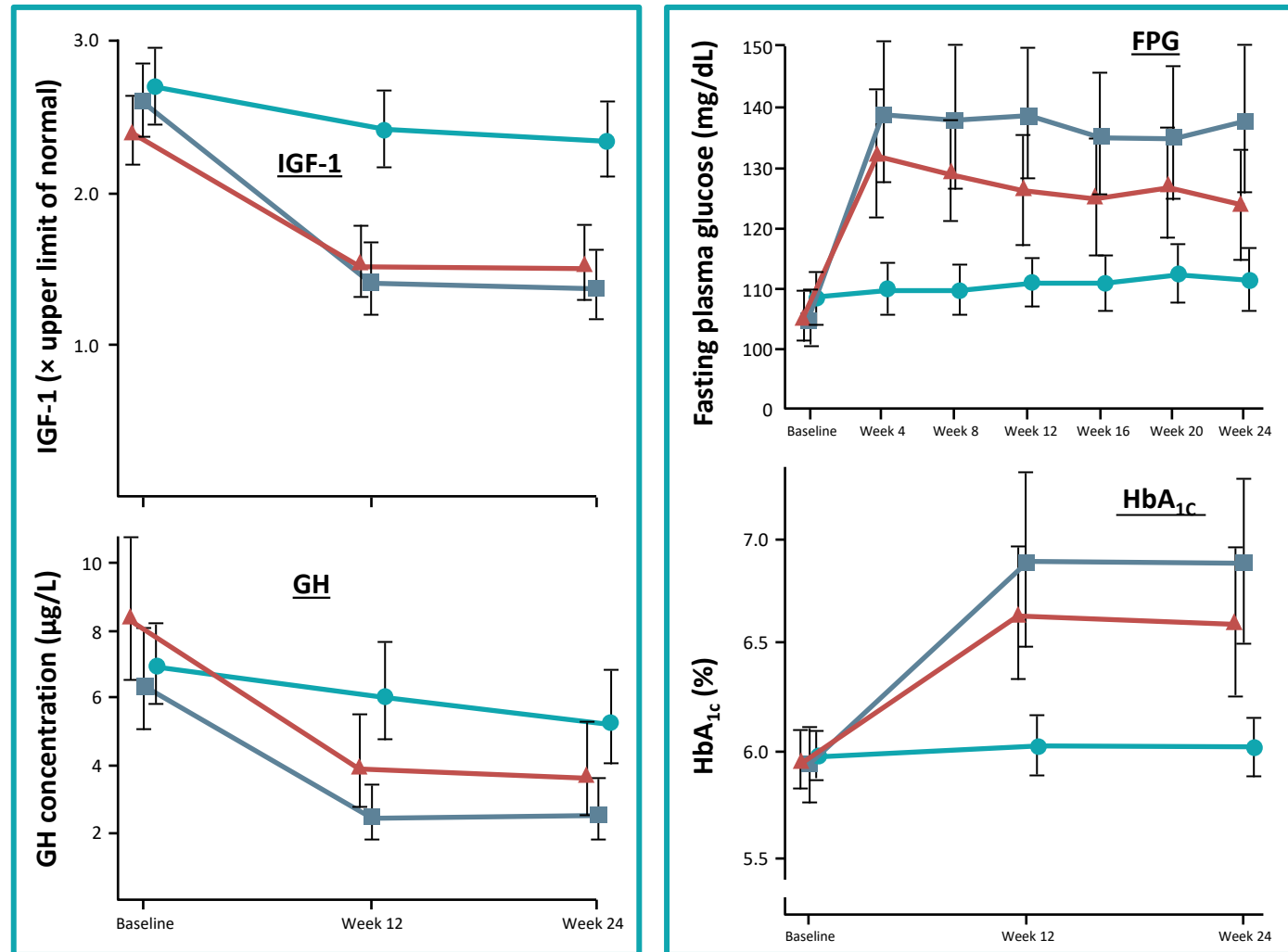


# PASIREOTIDE: A MULTIRECEPTOR-TARGETED SRL



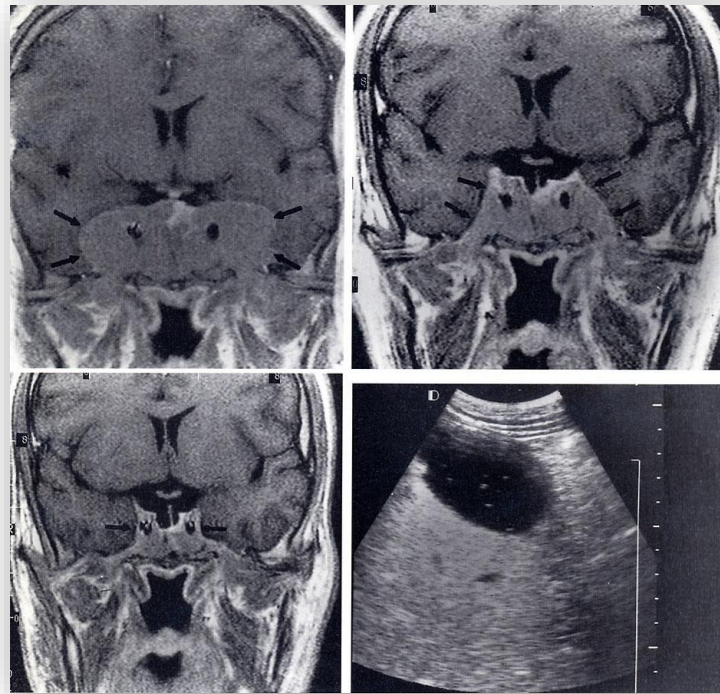
Affinity higher for sst<sub>5</sub> than octreotide and lanreotide,  
and similar for sst<sub>2</sub>

# PASIREOTIDE VS OCTREOTIDE OR LANREOTIDE IN INADEQUATELY CONTROLLED ACROMEGALY



▲ Pasireotide 40 mg  
■ Pasireotide 60 mg  
● Active control





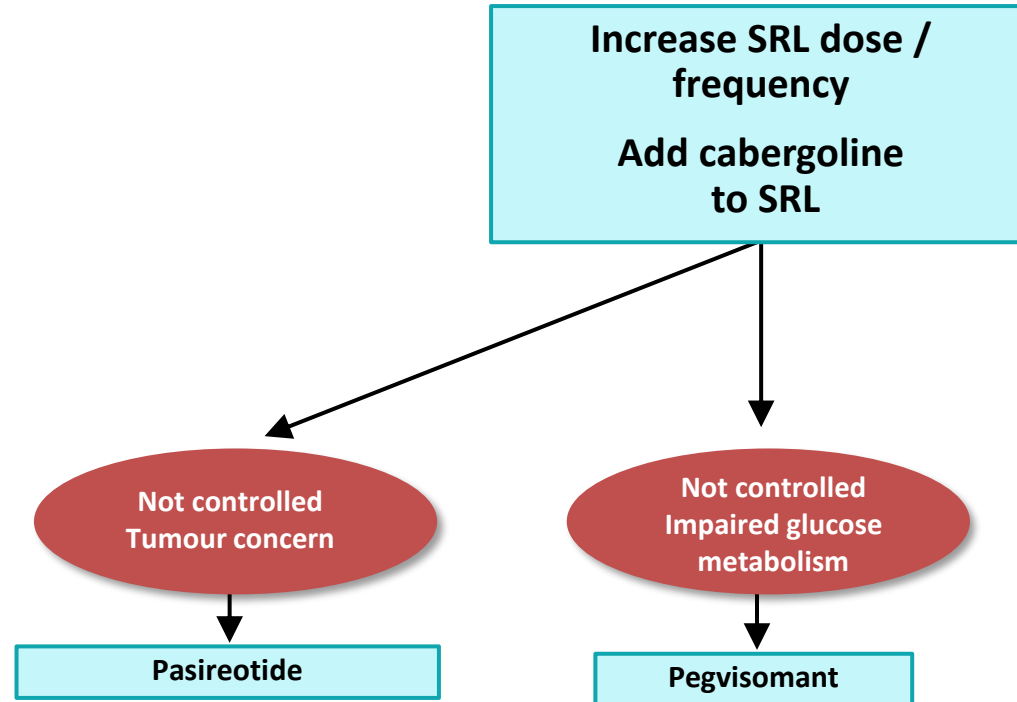
Doppman. The Endocrinologist. 1998

- **Advantages**
  - Rapid GH/IGF-1 control and symptom relief
  - No hypopituitarism
  - Tumour mass control

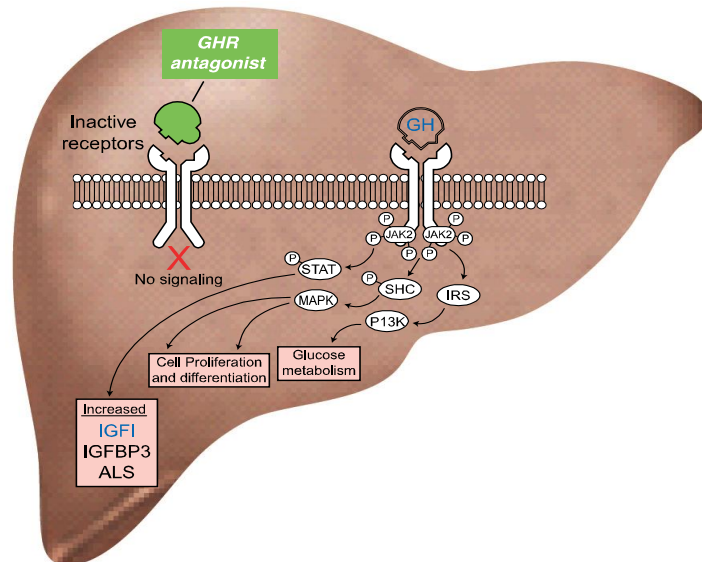
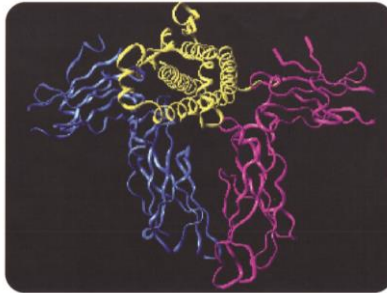
- **Adverse effects**
- **Gallbladder**
  - Gallstones or sludge
- **Gastrointestinal**
  - Diarrhoea
  - Nausea
  - Discomfort
- **Glucose**
  - Hypo/hyperglycaemia\*
- **Cardiac**
  - Sinus bradycardia
- **Other**
  - Injection site pain\*\*
  - Alopecia

- **Disadvantages**
  - Cure not permanent
  - Long-term treatment
  - Cost
  - Injection compliance\*\*

# INADEQUATE CONTROL WITH SRLS



# GH RECEPTOR ANTAGONIST



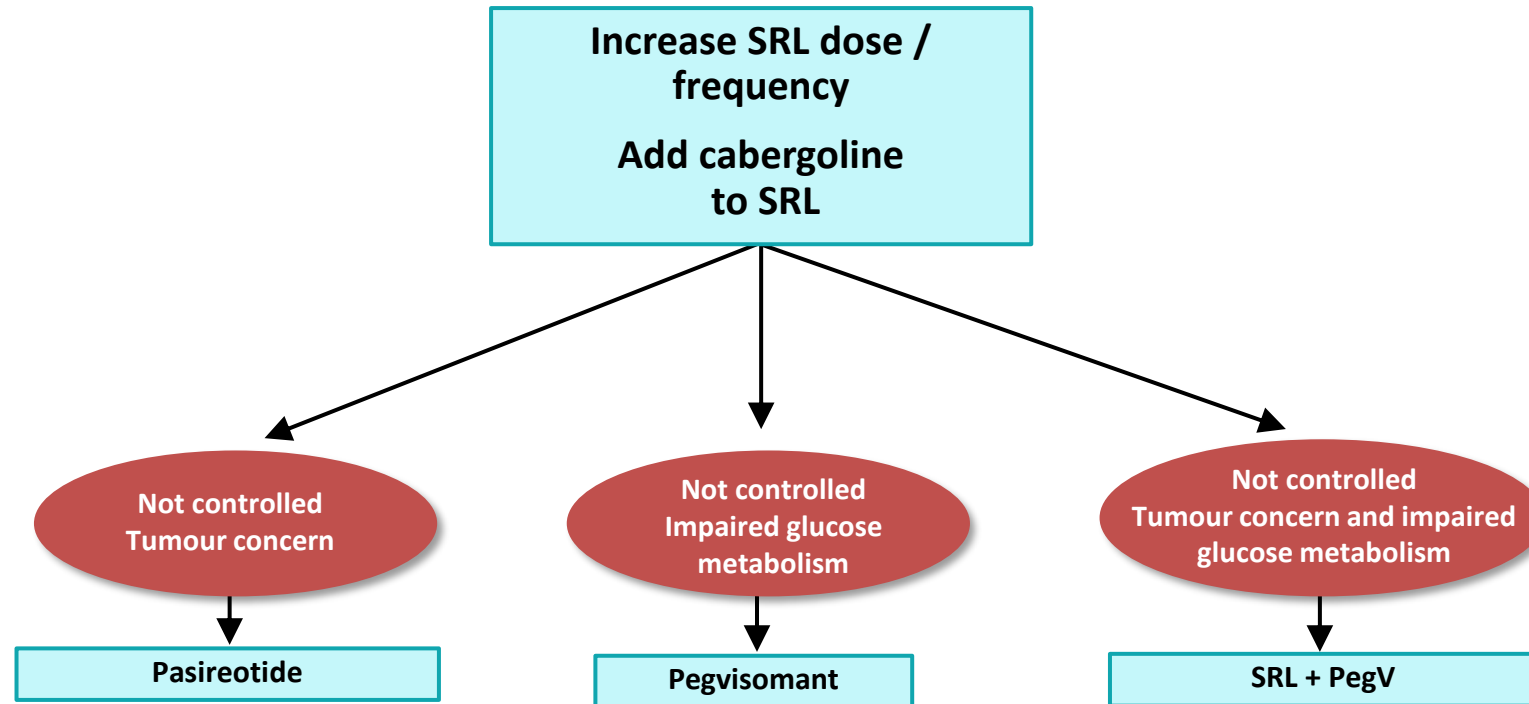
## Goals

- Normalise IGF-1
- Control symptoms
- **Efficacy (normal IGF-1):**
  - >70% at 20-40 mg/day

## Disadvantages

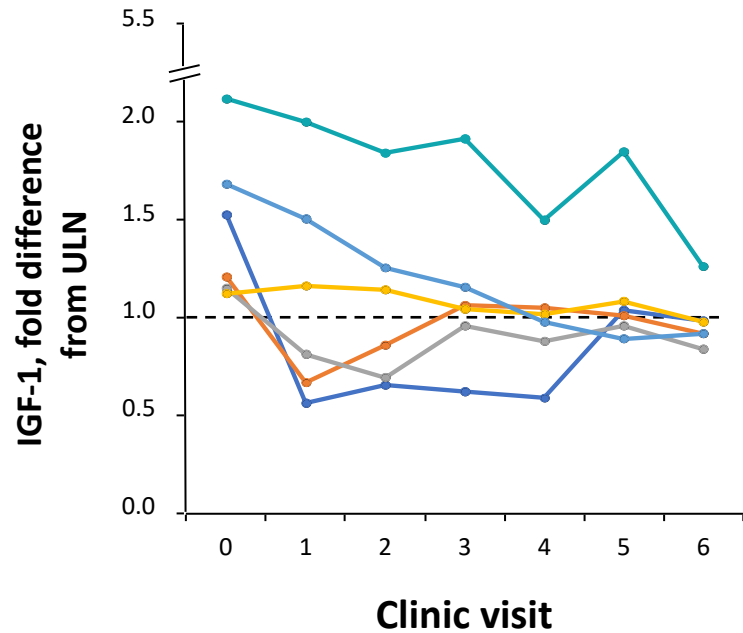
- Daily injection
- Elevated liver enzymes – rare
- Lipodystrophy – rare

# INADEQUATE CONTROL

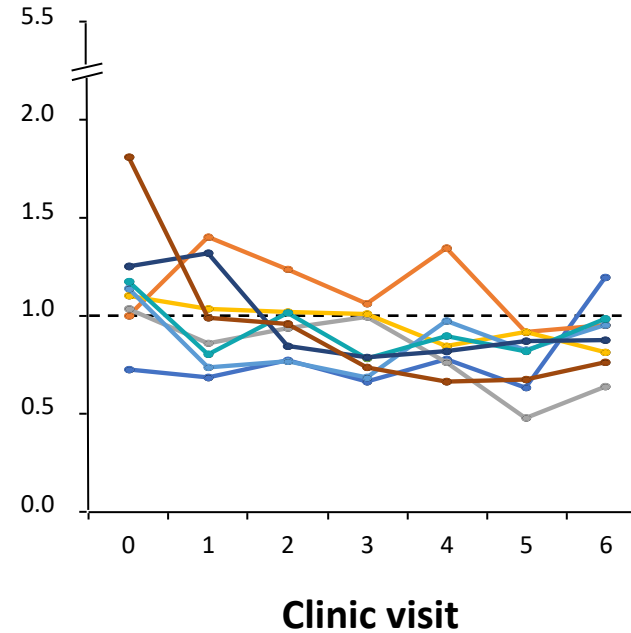


# CONTROL ACHIEVED IN 96% OF 52 PATIENTS UNCONTROLLED AT BASELINE

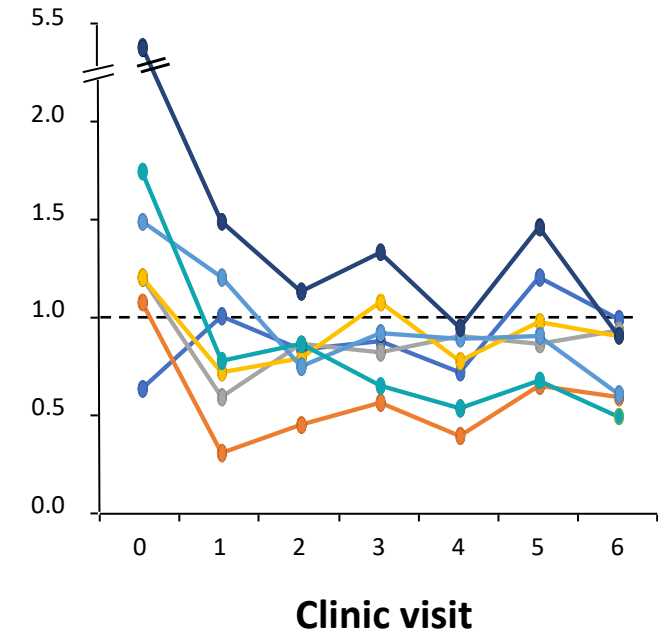
**High-dose SRL + weekly PegV**



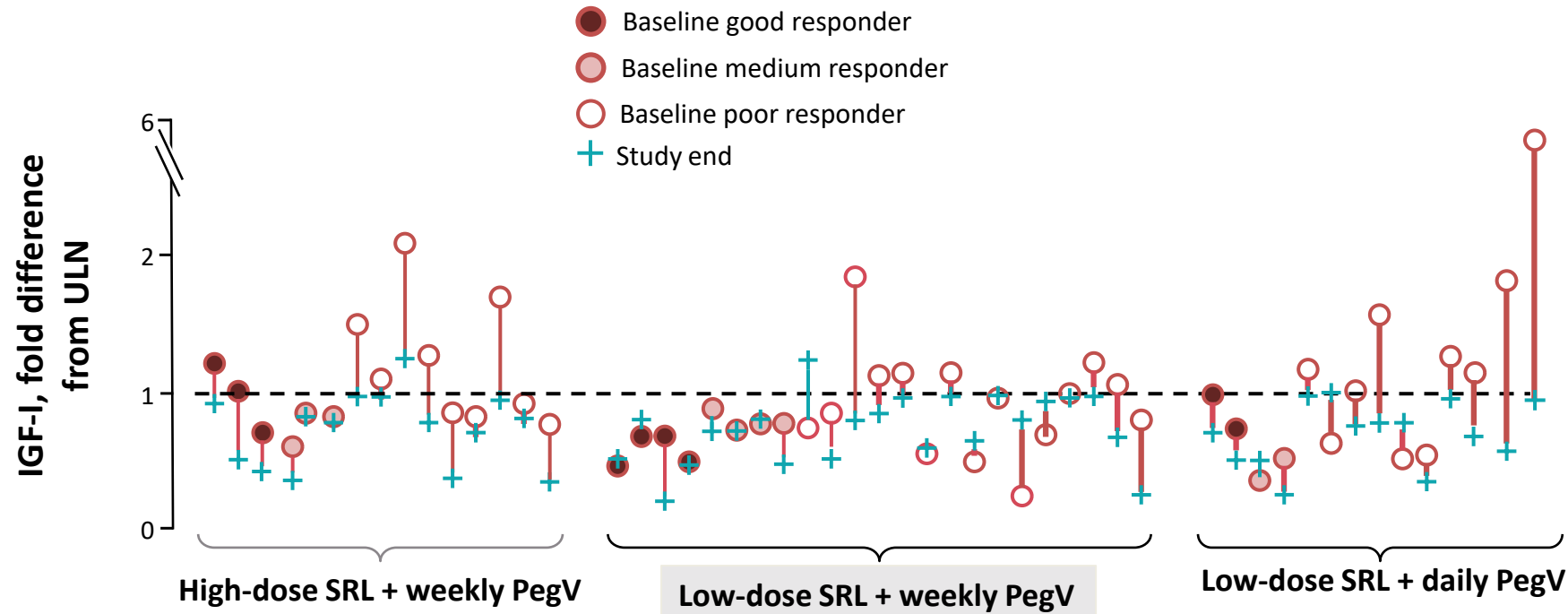
**Low-dose SRL + weekly pegV**



**Low-dose SRL + daily PegV**



# PROSPECTIVE RANDOMISED TRIAL COST-EFFECTIVENESS AND EFFICACY OF NOVEL COMBINATIONS



Control

14/15

22/23

14/14

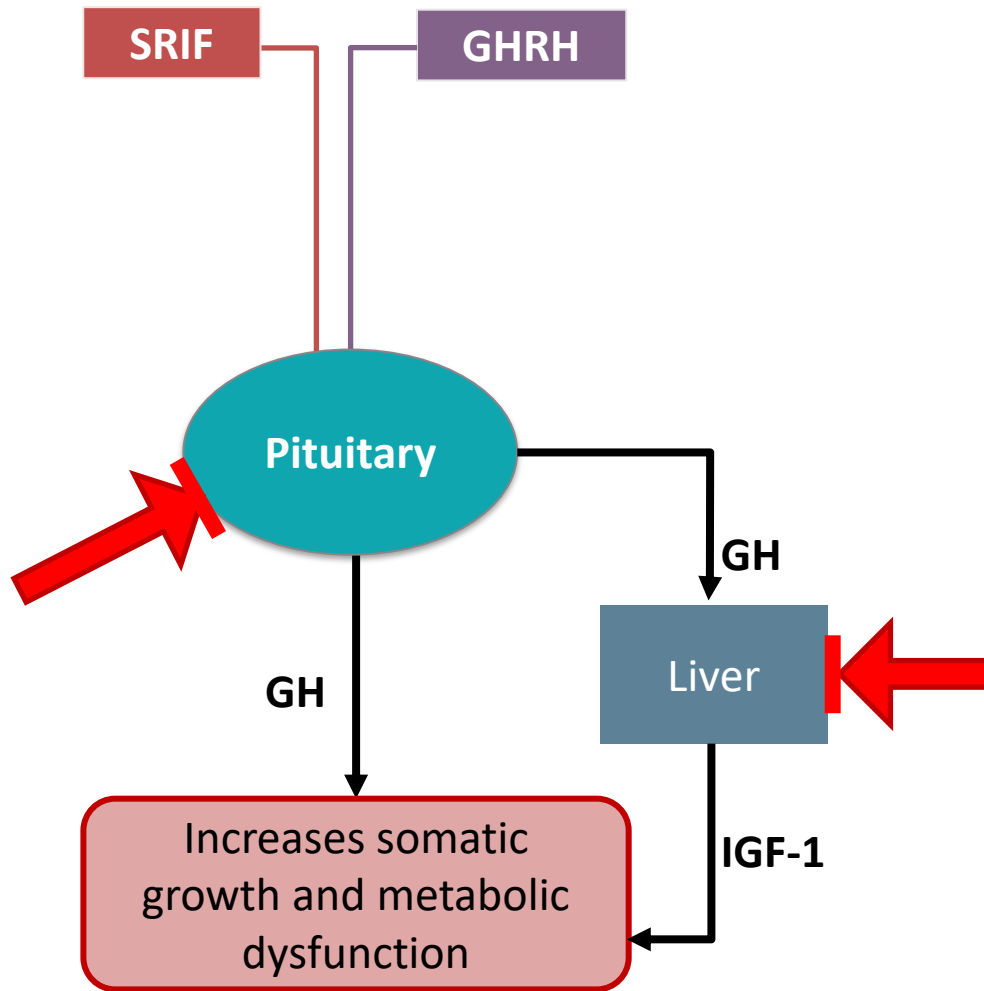
Monthly mean cost

\$14,261

\$9,837

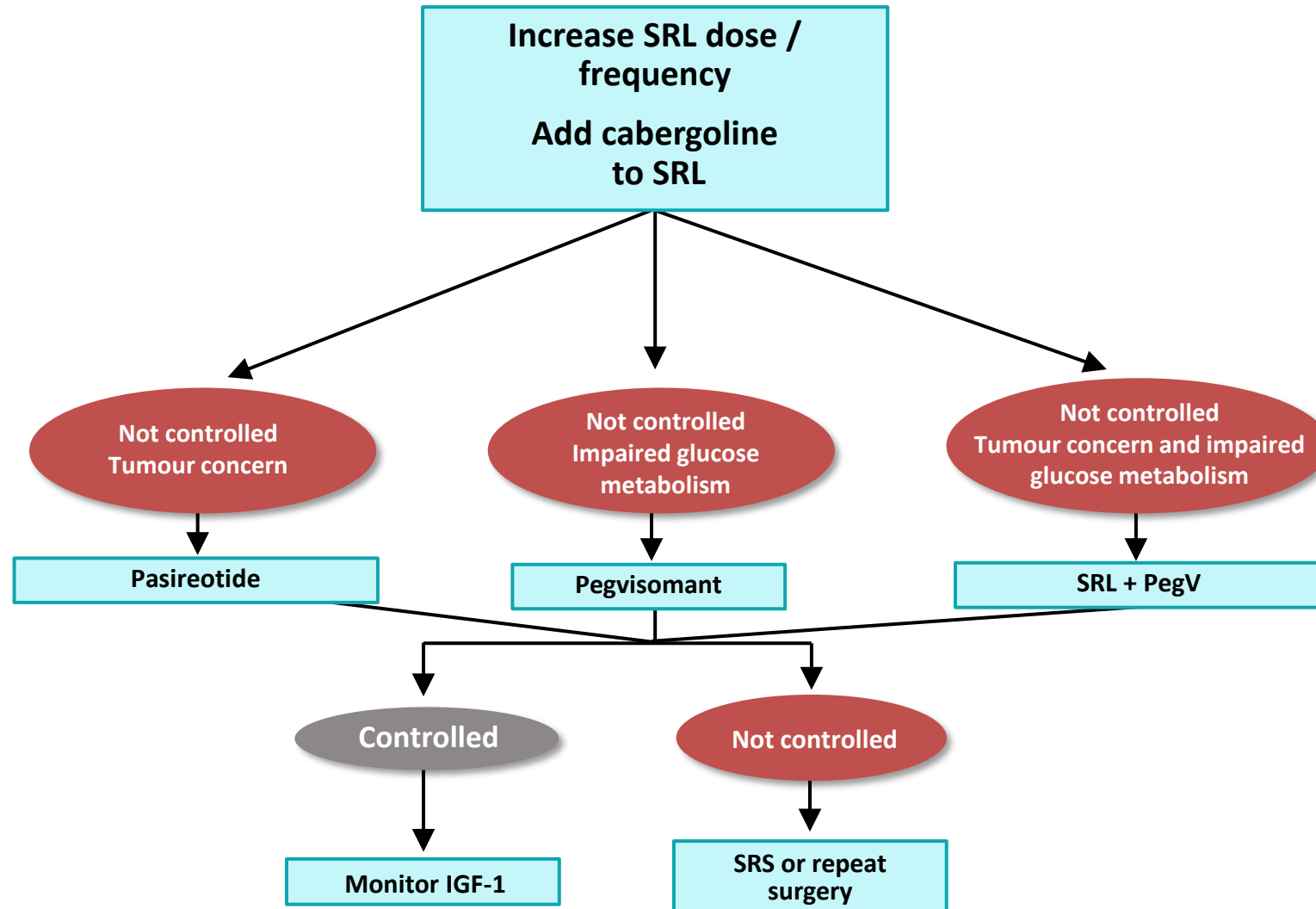
\$22,543

# COMBINED SRL AND PEGVISOMANT



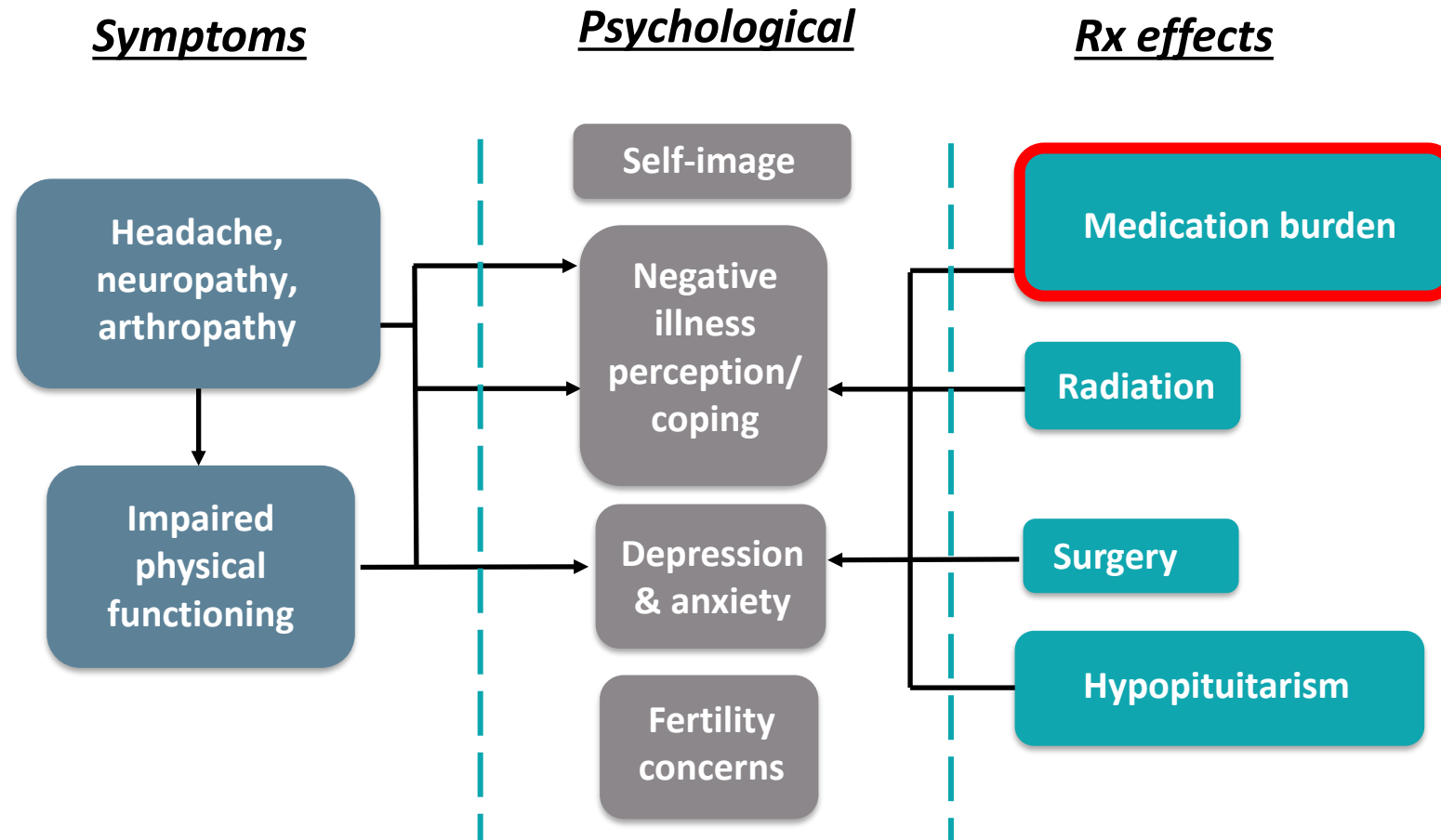
Morbidity	Improved
IGF-1	Controlled ~90%
Pituitary function	<i>Uncompromised</i>
Tumour Size	Controlled
Adverse Effects	Similar
Avoid less safe Rx	<i>Patient choice</i>

# ACROMEGALY MEDICAL CONTROL





# QUALITY OF LIFE

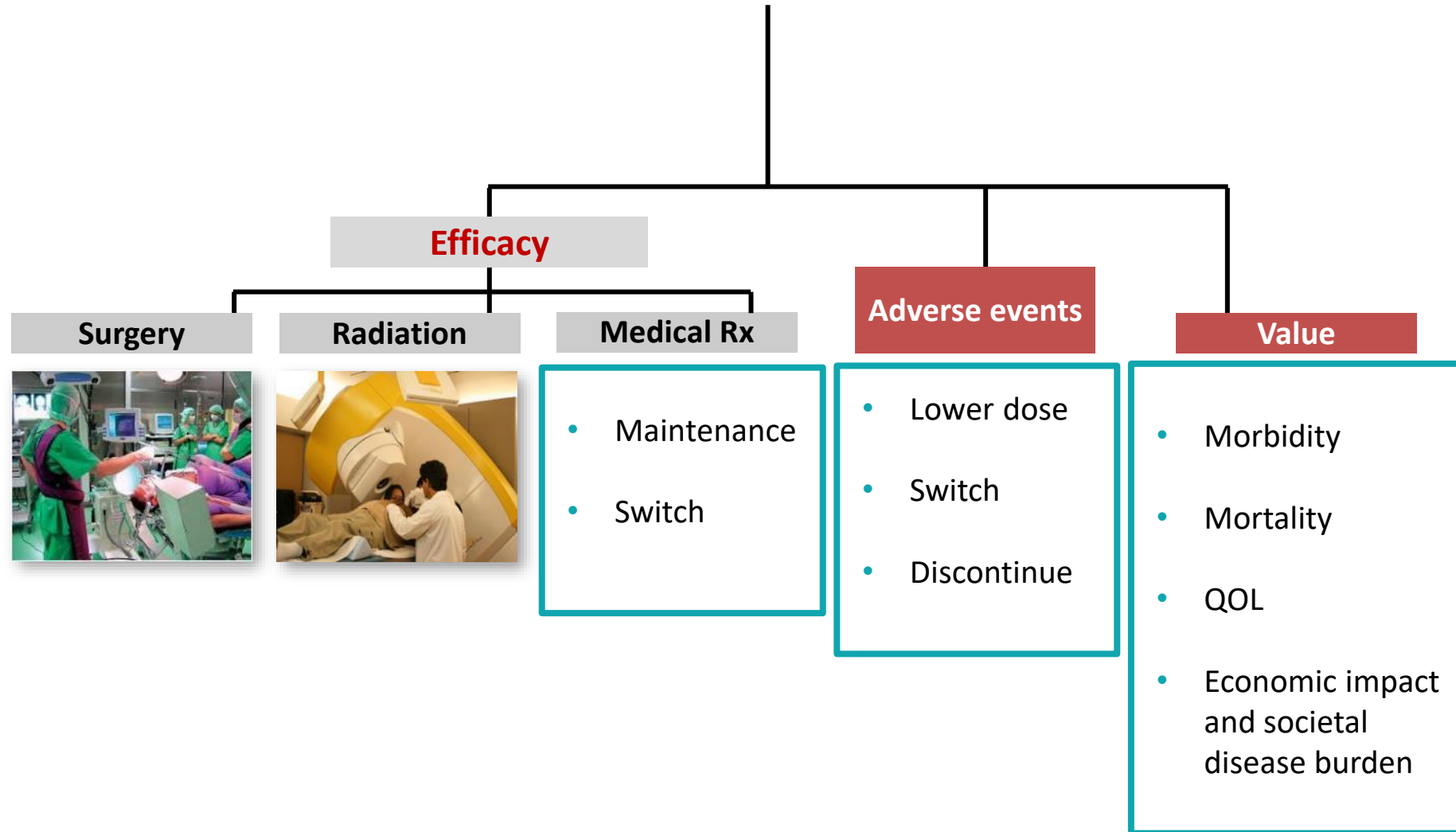


# MONITORING PATIENT-FOCUSED OUTCOMES

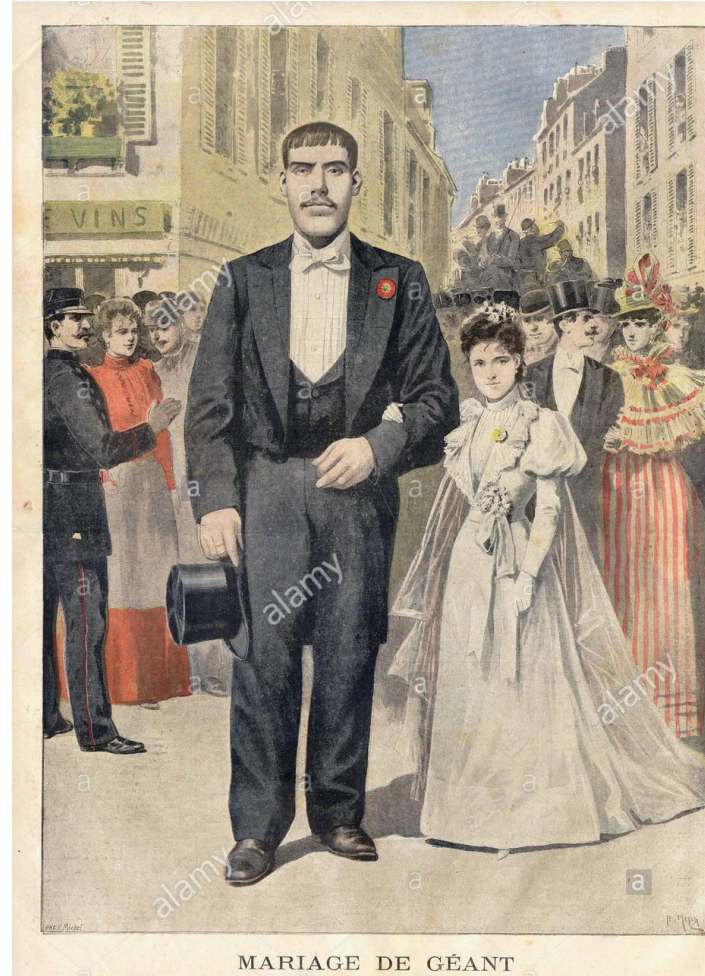
- Arthralgias and headache
- **Cardiac failure & hypertension**
- Diabetes
- Sleep apnoea
  
- Endocrine replacement
- Fertility
- Self-image and anxiety
- Maxillo-facial surgery
  
- Interpret laboratory testing
  
- **Side-effects of therapy!**



# TARGETED MANAGEMENT DECISIONS



# MARIAGE DE GEANT



MARIAGE DE GÉANT



POWERED BY COR2ED

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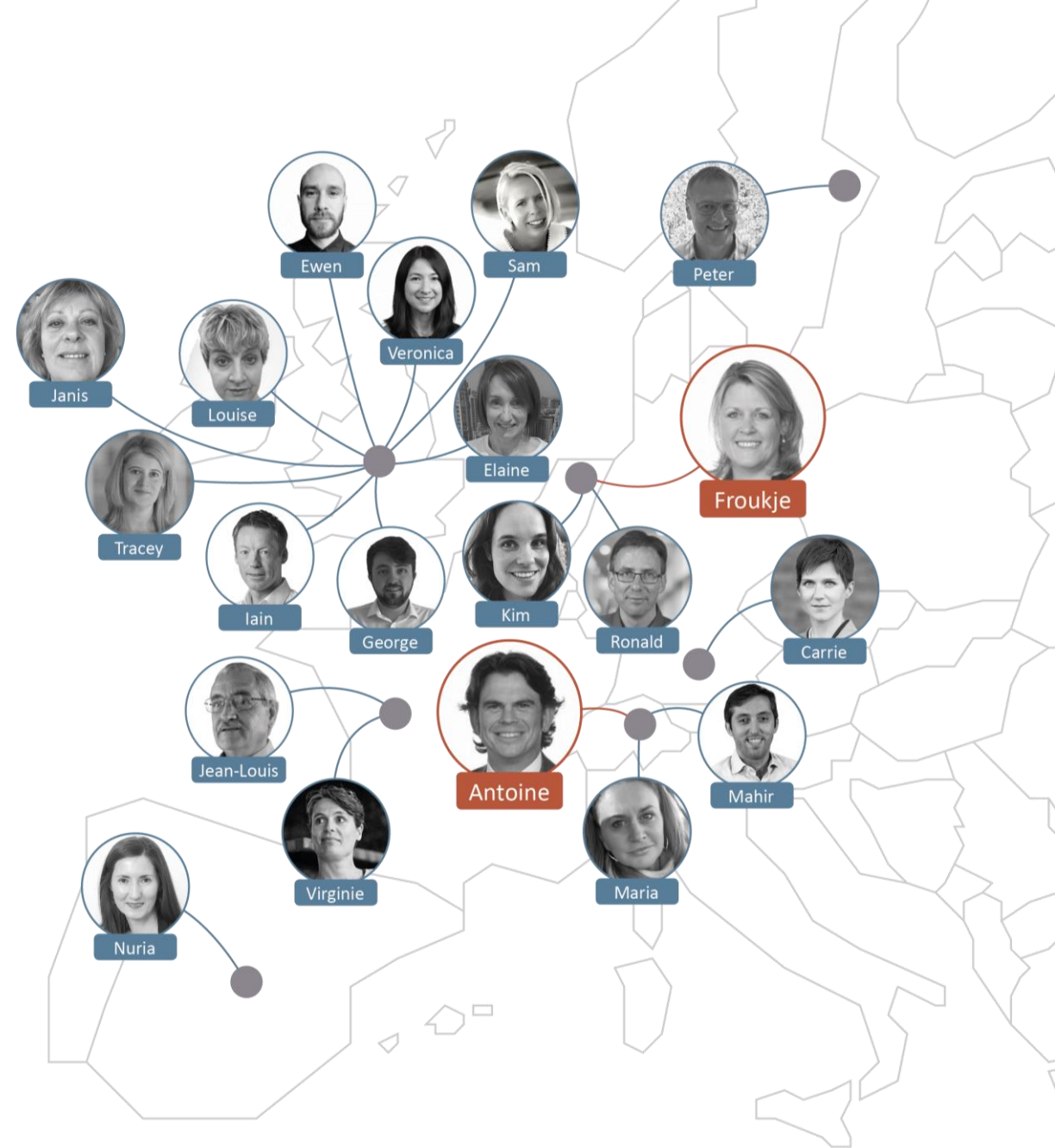
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